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(54) Title: RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siRNA)

(57) Abstract: The present invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with respiratory and pulmonary disease, such as severe acute respiratory syndrome (SARS) virus genes, using short interfering nucleic acid (siRNA) molecules. This invention also comprises compounds, compositions, and methods useful for modulating the expression and activity of SARS virus genes, or other genes involved in pathways of SARS virus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siRNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of SARS virus RNA.

**RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE
RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING
SHORT INTERFERING NUCLEIC ACID (siNA)**

This application claims the benefit of U.S. Provisional Application No. 5 60/462,874, filed April 15, 2003, and is a continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003. This application 10 is also a continuation-in-part of US Patent Application No. 10/427,160, filed April 30, 2003.

Reference is made to International Patent Application No. PCT/US03/05346, filed February 20, 2003, and International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 15 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002; U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 20 filed January 15, 2003. Reference is also made to International Patent Application No. PCT/US02/15876 filed May 17, 2002.

All the listed applications are hereby incorporated by reference herein in their entireties, including the drawings.

Field Of The Invention

25 The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of diseases and conditions that respond to the modulation of severe acute respiratory syndrome (SARS) associated coronavirus (SARS virus) gene expression and/or activity. The present invention also concerns compounds, compositions, and methods relating to conditions and diseases that respond to the 30 modulation of expression and/or activity of genes involved in SARS virus pathways of

gene expression, including cellular genes that are involved in SARS virus infection. Specifically, the invention comprises small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of 5 mediating RNA interference (RNAi) against severe acute respiratory syndrome (SARS) associated coronavirus gene expression.

Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an 10 admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Fire *et al.*, 1998, *Nature*, 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951; Lin *et al.*, 1999, *Nature*, 402, 128-129; Sharp, 1999, *Genes &* 15 *Dev.*, 13:139-141; and Strauss, 1999, *Science*, 286, 886). The corresponding process in plants (Heifetz *et al.*, International PCT Publication No. WO 99/61631) is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression 20 of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or 25 viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from other known mechanisms involving double stranded RNA-specific ribonucleases, such as the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non- 30 specific cleavage of mRNA by ribonuclease L (see for example US Patent Nos.

6,107,094; 5,898,031; Clemens *et al.*, 1997, *J. Interferon & Cytokine Res.*, 17, 503-524; Adah *et al.*, 2001, *Curr. Med. Chem.*, 8, 1189).

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer (Bass, 2000, *Cell*, 101, 235; Zamore *et al.*, 2000, *Cell*, 101, 25-33; Hammond *et al.*, 2000, *Nature*, 404, 293). Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2000, *Cell*, 101, 235; Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). Dicer has also been implicated in the excision of 21 and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494 and Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide

overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also 5 shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to 10 maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell*, 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported 15 to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164). In addition, Elbashir *et al.*, *supra*, also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, International PCT Publication No. WO 00/44914, and Beach *et* 20 *al.*, International PCT Publication No. WO 01/68836 preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.*, 25 Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications 30 would be tolerated in dsRNA molecules.

- Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, tested certain chemical modifications targeting the unc-22 gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that RNAs with two phosphorothioate modified bases also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.
- The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila* *in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes. Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA

molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plaetinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules. Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Pachuck *et al.*, International PCT Publication No. WO 00/63364, describe certain long (at least 200 nucleotide) dsRNA constructs. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050 and 1998, *PNAS*, 95, 13959-13964, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the unc-22 gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al.*, International PCT Publication No. WO 01/53475, describe certain methods for isolating a Neurospora silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*,

International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.* International PCT Publications Nos. WO 02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, *Antisense & Nucleic Acid Drug Development*, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, *RNA*, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules.

McCaffrey *et al.*, 2002, *Nature*, 418, 38-39, describes the use of certain siRNA constructs targeting a chimeric SARS NS5B protein/luciferase transcript in mice.

Randall *et al.*, 2003, *PNAS USA*, 100, 235-240, describe certain siRNA constructs targeting SARS RNA in Huh7 hepatoma cell lines.

SUMMARY OF THE INVENTION

This invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with the development or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and/or other disease states associated with SARS virus infection, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful

for modulating the expression and activity of severe acute respiratory syndrome (SARS) associated coronavirus or genes involved in severe acute respiratory syndrome (SARS) associated coronavirus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of severe acute respiratory syndrome (SARS) associated coronavirus. For convenience, all forms of the small nucleic acid molecules of the invention (e.g., siRNA, dsRNA, micro-RNA, etc.) 10 are referred to herein as "siNA," unless expressly stated otherwise.

A siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating repeat expansion gene expression or activity in cells by RNA interference (RNAi). The 15 use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant 20 invention are useful reagents and are useful in methods for a variety of therapeutic, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of 25 gene(s) encoding SARS virus. Specifically, the present invention comprises siNA molecules that modulate the expression of SARS proteins, for example, proteins encoded by SARS virus genome, such as Genbank Accession Nos. in Table I.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of 30 genes representing cellular targets for SARS virus infection, such as cellular receptors,

cell surface molecules, cellular enzymes, cellular transcription factors, and/or cytokines, second messengers, and cellular accessory molecules.

Due to the high sequence variability of the SARS genome, selection of siNA molecules for broad therapeutic applications preferably involve the conserved regions of the SARS genome. In one embodiment, the present invention comprises siNA molecules that target the conserved regions of the SARS genome, such as the polymerase encoding region of the SARS virus genomic RNA. Therefore, siNA molecules of the invention are designed to target all the different isolates of SARS. siNA molecules designed to target conserved regions of various SARS isolates enable efficient inhibition of SARS replication in diverse patient populations and ensure the effectiveness of the siNA molecules against SARS quasi species that evolve due to mutations in the non-conserved regions of the SARS genome. Therefore, a single siNA molecule can be targeted against all isolates of SARS by designing the siNA molecule to interact with conserved nucleotide sequences of SARS (such conserved sequences are expected to be present in the RNA of all SARS isolates).

In one embodiment, a siNA molecule is designed to target the 3'-untranslated region and/or the shared leader sequence of genomic SARS RNA transcripts. Because SARS coronavirus mRNAs are nested with the genomic RNA and share common 3' region and polyA region, a single siNA targeting the 3'-end can target all transcripts plus the genomic RNA.

In one embodiment, a siNA molecule of the invention targets both the plus (genomic) strand RNA and minus strand RNA of the SARS virus. Because the SARS virus generates a minus strand RNA from plus strand genomic RNA, a double stranded siNA molecule targeting the plus strand will also target the minus strand, thus allowing a single double-stranded siNA to target both the plus (genomic) and the minus strand of the SARS virus. For example, a double stranded siNA molecule targeting the 3'-end of the SARS virus genomic strand will also target the 3'-end of the the minus strand, thus allowing a single double-stranded siNA to target both the plus and the minus strand of the SARS virus.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus and/or cellular proteins associated with the maintenance or development of SARS virus infection and/or acute respiratory failure, viral pneumonia,

5 such as genes encoding sequences comprising those sequences referred to by GenBank Accession Nos. shown in Table I, referred to herein generally as SARS. The description below of the various aspects and embodiments of the invention is provided with reference to exemplary severe acute respiratory syndrome (SARS) associated coronavirus genes, generally referred to herein as SARS. However, such reference is meant to be

10 exemplary only and the various aspects and embodiments of the invention are also directed to other genes that express alternate SARS genes, such as mutant SARS genes, splice variants of SARS genes, and genes encoding different strains of SARS, as well as as cellular targets for SARS, such as those described herein. The various aspects and embodiments are also directed to other genes involved in SARS pathways, including

15 genes that encode cellular proteins involved in the maintenance and/or development of SARS virus infection and/or acute respiratory failure or other genes that express other proteins associated with SARS virus infection, such as cellular proteins that are utilized in the SARS life-cycle. Such additional genes can be analyzed for target sites using the methods described herein for SARS. Thus, the inhibition and the effects of such

20 inhibition of the other genes can be performed as described herein. In other words, the term "SARS" as it is defined herein below and recited in the described embodiments, is meant to encompass genes associated with the development or maintenance of SARS virus infection, such as genes which encode SARS polypeptides, including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as

25 well as cellular genes involved in SARS pathways of gene expression, replication, and/or SARS activity. Also, the term "SARS" as it is defined herein and recited in the described embodiments, is meant to encompass SARS viral gene products and cellular gene products involved in SARS virus infection, such as those described herein. Thus, each of the embodiments described herein with reference to the term "SARS" are

30 applicable to all of the virus, cellular and viral protein, peptide, polypeptide, and/or polynucleotide molecules covered by the term "SARS" as that term is defined herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a severe acute respiratory syndrome virus (e.g., SARS) gene, wherein said siNA molecule comprises about 19 to about 23 base pairs. Preferably the number of based pairs in the siNA 5 molecule is 18, 19, 20, 21, 22, 23, or 24.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene 10 comprises SARS non-coding sequence or regulatory elements involved in SARS gene expression.

In one embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having SARS encoding sequence, such as those sequences having GenBank 15 Accession Nos. shown in **Table I**. In another embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other SARS encoding sequence, for example other mutant SARS genes not shown in **Table I** but known in the art to be associated with respiratory and/or pulmonary disease, SARS virus infection 20 and/or acute respiratory failure, viral pneumonia, impeded respiration, respiratory distress syndrome, pulmonary hypertension, or pulmonary vasoconstriction. Chemical modifications as shown in **Tables III and IV** or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes nucleotide sequence that can interact with nucleotide 25 sequence of a SARS gene and thereby mediate silencing of SARS gene expression, for example, wherein the siNA mediates regulation of SARS gene expression by cellular processes that modulate the chromatin structure of the SARS gene and prevent transcription of the SARS gene.

In another embodiment, the invention features a siNA molecule comprising 30 nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of

a SARS gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a SARS gene sequence or a portion thereof.

In one embodiment, the antisense region of SARS siNA constructs can comprise a
5 sequence complementary to sequence having any of SEQ ID NOS. 1-1651 or 3303-3318. In one embodiment, the antisense region can also comprise sequence having any of SEQ ID NOS. 1652-3302, 3319-3326, 3335-3342, 3351-3358, 3367-3374, 3376, 3378, 3380, 3383, 3385, 3387, 3389, or 3392. In another embodiment, the sense region of the SARS constructs can comprise sequence having any of SEQ ID NOS. 1-1651, 3303-3310, 3311-
10 3318, 3327-3334, 3343-3350, 3359-3366, 3375, 3377, 3379, 3381, 3382, 3384, 3386, 3388, 3390, or 3391.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOS. 1-3392. The sequences shown in SEQ ID NOS: 1-3392 are not limiting. A siNA molecule of the invention can comprise any contiguous SARS sequence (e.g., about 19
15 to about 25, or about 19, 20, 21, 22, 23, 24 or 25 contiguous SARS nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in Table I. Chemical modifications in Tables III and IV and
20 described herein can be applied to any siNA construct of the invention. siNA molecules of the invention are unmodified or have up to all nucleotides modified with modifications according to Tables III and IV.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or
25 30) nucleotides, wherein the antisense strand is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences with at least about 19 complementary nucleotides.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a 5 sense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein said sense region and said antisense region comprise a linear molecule with at least about 19 complementary nucleotides.

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence 10 or a portion thereof encoding a SARS protein. The siNA further comprises a sense strand, wherein said sense strand comprises a nucleotide sequence of a SARS gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence 15 encoding a SARS protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a SARS gene or a portion thereof.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a SARS gene. Because SARS genes can 20 share some degree of sequence homology with each other, siNA molecules can be designed to target a class of SARS genes or alternately specific SARS genes by selecting sequences that are either shared among different SARS targets (e.g., differnet viral strains) or alternatively that are unique for a specific SARS target (e.g., a particular viral strain). Therefore, in one embodiment, the siNA molecule can be designed to target 25 conserved regions of SARS RNA sequences having homology among several SARS genes so as to target several SARS genes (e.g., different SARS isoforms, splice variants, mutant genes etc.) with one siNA molecule. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific SARS RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi 30 activity.

- In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplexes containing about 19 base pairs between oligonucleotides comprising about 19
- 5 to about 25 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplexes with overhanging ends of about about 1 to about 3 (e.g., 1, 2, 3, or 4) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs.
- 10 In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for SARS expressing nucleic acid molecules, such as RNA encoding a SARS protein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides,
- 15 "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al.*, *supra*,
- 20 applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides

25 can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%,

30 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA

molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total 5 number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene. In one embodiment, a double stranded siNA molecule comprises one or more chemical 10 modifications and each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule comprises about 19 to about 23 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 15 27, 28, or 29) nucleotides, wherein each strand comprises about 19 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the SARS gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence 20 substantially similar to the nucleotide sequence of the SARS gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the SARS gene or a portion 25 thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In one embodiment, the antisense region and the sense region each comprise about 19 to about 23 (e.g. about 19, 20, 21, 22, or 23) nucleotides, wherein the antisense region comprises about 19 nucleotides that are complementary to nucleotides of the sense 30 region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus minus strand RNA. In another embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus plus strand RNA.

10 In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule of the invention comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising Stab00-Stab22 or any combination thereof (see Table IV)) and/or any length described herein can comprise blunt ends or
15 ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e., where a blunt end does not have any overhanging nucleotides. In a non-limiting example, a blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another example,
20 a siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises one blunt end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt
25 ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 18 to about 30 nucleotides (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA
30 molecule can comprise mismatches, bulges, loops, or wobble base pairs, for example, to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are 5 complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the 10 antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein 15 the siNA molecule comprises about 19 to about 21 base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a 20 nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the 25 nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

In one embodiment, a siNA molecule of the invention comprises an antisense 5 region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 19 to about 23 nucleotides and the antisense region 10 comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS gene, or a 15 portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In another embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the 20 antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, the invention features a double-stranded short interfering 25 nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA 30 molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine

nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides.

- 5 In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In
10 another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein
15 the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In another embodiment, the terminal cap moiety is an inverted
20 deoxy abasic moiety or glyceryl moiety. In another embodiment, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. The siNA can be, for example, of length between about 12 and about 36 nucleotides. In
25 another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another
30 embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-

deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified 5 internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a 10 siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'- 15 deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro- uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another 20 embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected 25 locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region 30 comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a

nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy-purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the 5 antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 10 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of a SARS transcript having sequence unique to a particular SARS disease related allele, such as sequence comprising a SNP associated with the disease specific allele. As such, the antisense region of a siNA 15 molecule of the invention can comprise sequence complementary to sequences that are unique to a particular allele to provide specificity in mediating selective RNAi against the disease related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein 20 the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides 25 of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the 30 other fragment of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the

RNA encoded by the SARS gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the SARS gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally include a phosphate group.

- 5 In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SARS RNA sequence (e.g., wherein said target RNA sequence is encoded by a SARS gene involved in the SARS pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 21 nucleotides long.
- 10 Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in Table IV in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, or Stab 18/20.
- 15 In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a SARS RNA via RNA interference, wherein each strand of said RNA molecule is about 21 to about 23 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the SARS RNA for the RNA molecule to direct cleavage of the
- 20 SARS RNA via RNA interference; and wherein at least one strand of the RNA molecule comprises one or more chemically modified nucleotides described herein, such as deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-O-methoxyethyl nucleotides etc.

25 In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a SARS gene,

wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 18 to about 28 or more (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or more) nucleotides long.

In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA that encodes a protein or portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other

strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 18 5 to about 29 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein each strand comprises at least about 18 nucleotides that are complementary to the nucleotides of the other strand. In another embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a 10 second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In yet another embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense 15 region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the 20 antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine 25 nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense 30 strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein each of the two strands of the siNA molecule comprises about 21 nucleotides. In one embodiment, about 21 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In another embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof. In another embodiment, about 21 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the SARS RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the SARS RNA or a portion thereof that is present in the SARS RNA.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of

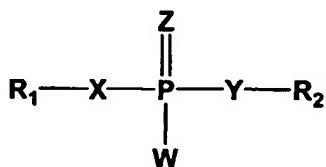
a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native 5 unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments 10 of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or 15 backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a 20 nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise 25 sequence complementary to a RNA or DNA sequence encoding SARS and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.

In one embodiment, the nucleotide sequence of the antisense strand or a portion thereof of a siNA molecule of the invention is complementary to the nucleotide sequence of a SARS RNA or a portion thereof that is present in the RNA of all SARS isolates.

In one embodiment, the invention features a chemically-modified short interfering 5 nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:

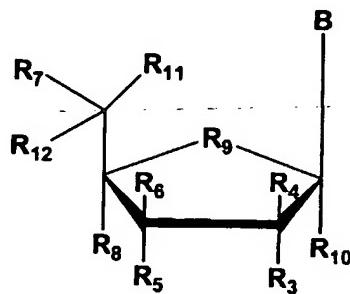


10 wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of 15 the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, Nucleic Acids Research, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present 20 in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more 25 (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine

nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified 5 internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering 10 nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:



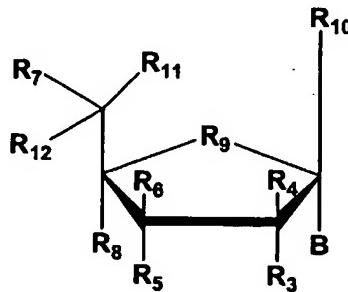
15 wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-O SH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O- 20 aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH₂, S=O, CHF, or CF₂, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a 25 non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine,

pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the 5 sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

15 In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:

20



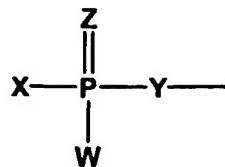
wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, 25 NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-

aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH₂, S=O, CHF, or CF₂, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

- 5 In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a strand complementary to a target RNA, wherein the siNA molecule comprises an all RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary
- 10 strand wherein the siNA molecule also comprises about 1 to about 3 (e.g., about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (e.g., about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA
- 15 molecule having chemical modifications having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and

5' -ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (e.g., about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting 5 example, an exemplary siNA molecule of the invention can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate 10 internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more 15 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate 20 internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the 25 antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense 30 strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, or more) 2'-deoxy,

2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more

5 phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3,

10 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different

15 strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more

phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or 5 more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or 10 more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand. In another 15 embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both 20 of the 3' and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5' 25 internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands 30 of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (e.g., about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36 to about 70 (e.g., about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (e.g., about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 42 to about 50 (e.g., about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

30 In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (e.g., about 25, 26, 27, 28, 29, 30, 31,

32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (e.g., about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to 10 about 23 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another 15 embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (e.g., about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 20 or 50) nucleotides in length having about 3 to about 20 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (e.g., about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is 25 30

biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising 5 sense and antisense regions, wherein the antisense region is about 16 to about 25 (e.g., about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region is about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more 10 chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 22 (e.g., about 18, 19, 20, 21, or 22) nucleotides in length and 15 wherein the sense region is about 3 to about 15 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetric double stranded siNA 20 molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

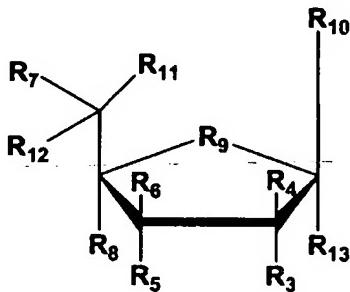
In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (e.g., about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (e.g., about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical 25 modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (e.g., about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a 30 chemical modification having any of Formulae I-VII or any combination thereof,

wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable.

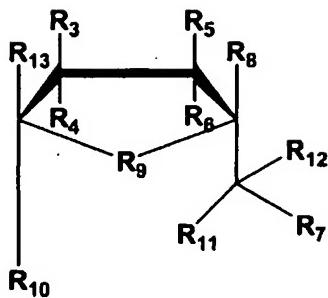
- 5 For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

- In one embodiment, a siNA molecule of the invention comprises at least one (e.g.,
10 about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



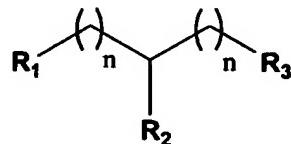
- wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.
15

- 20 In one embodiment, a siNA molecule of the invention comprises at least one (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH₂, S=O, CHF, or CF₂, and either R2, R3, R8 or R13 serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each n is independently an integer from 1 to 12, each R1, R2 and R3 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or a group having Formula I, and R1, R2 or R3 serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups, n = 1, and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in Figure 10).

In another embodiment, a moiety having any of Formula V, VI or VII of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, a moiety having Formula V, VI or VII can be present at the 10 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic 15 residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for 20 example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA 25 molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-

2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality 5 of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-10 2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality 15 of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-20 2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a 25 plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-30 2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (e.g., one or more or all) purine

nucleotides present in the sense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (e.g., one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or

more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

- In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

- In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system comprising a sense region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). The sense region and/or the antisense region can have a terminal cap modification, such as any modification described herein or shown in Figure 10, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the

sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or 5 thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in Figures 4 and 5 and Tables III and IV herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine 10 nucleotides are 2'-O-methyl purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Also, in any of these embodiments, one 15 or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Additionally, in any 20 of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) 25 nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of 30 the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring

ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, 5 preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2'-O, 4'-C-methylene-(D-ribofuranosyl) nucleotides); 2'- 10 methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example Figure 10) such as an 15 inverted deoxyabasic moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification 20 comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA 25 molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the 30 conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any

combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, filed July 22, 2002, incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the invention can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin.*

Mol. Ther., 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, 5 polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, 18:6353 and *Nucleic Acids Res.* 1987, 15:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, 113:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, 113:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, 10 21:2585 and *Biochemistry* 1993, 32:1751; Durand *et al.*, *Nucleic Acids Res.* 1990, 18:6353; McCurdy *et al.*, *Nucleosides & Nucleotides* 1991, 10:287; Jschke *et al.*, *Tetrahedron Lett.* 1993, 34:301; Ono *et al.*, *Biochemistry* 1991, 30:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz 15 and Verdine, *J. Am. Chem. Soc.* 1991, 113:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not 20 contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted *in vitro* system, wherein one or both strands of the siNA molecule that are assembled from 25 two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA comprise separate oligonucleotides not having any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonucleotide where the 30 sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as described herein, wherein the oligonucleotide does not have any

ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presence of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within the siNA can 5 include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA 10 molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a 15 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the single stranded siNA molecule of the invention comprises about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all 20 the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA 25 molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 30 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine

nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA

5 optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal

10 phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense

15 and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or

20 alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation

25 (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, the invention features a method for modulating the expression

30 of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the

siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

10 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

15 In another embodiment, the invention features a method for modulating the expression of two or more SARS genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the SARS genes and
20 wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

25 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA

molecule into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, siNA molecules of the invention are used as reagents in *ex vivo* applications. For example, siNA reagents are introduced into tissue or cells that are transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in vivo. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeting a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate

the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

5 In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular
10 organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS genes in that organism.

15 In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of
20 the SARS gene in the organism. The level of SARS protein or RNA can be determined as is known in the art.

25 In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b)
introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism. The level of SARS protein or RNA can be determined as is known in the art.

30 In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the

invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) contacting the cell *in vitro* or *in vivo* with the siNA molecule under
10 conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b)
15 contacting the cell of the tissue explant derived from a particular organism with the siNA molecule under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that
20 organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS
25 genes in that organism.
30

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b)

5 introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA

10 comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising contacting the organism with a siNA

15 molecule of the invention under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising contacting the organism with one or more siNA molecules of the invention under conditions suitable to

20 modulate the expression of the SARS genes in the organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (e.g., SARS) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs

25 include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish

30 among the functions of gene family members. For example, a protein that contains an

alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as SARS family genes. As such, siNA molecules targeting multiple SARS targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example SARS genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in Table I.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of

a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described 5 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the 10 art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of 4^N , where N represents the number of base paired nucleotides in each of the siNA construct 15 strands (eg. for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be 4^{19}); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target SARS RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the 20 siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 7 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of SARS RNA are 25 analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target SARS RNA sequence. The target SARS RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

30 In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets

of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In 5 another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. Fragments of target RNA are 10 analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

15 By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation 20 of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a 25 composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for 30

treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a
5 method for reducing or preventing tissue rejection in a subject comprising administering to the subject a composition of the invention under conditions suitable for the reduction or prevention of tissue rejection in the subject.

In another embodiment, the invention features a method for validating a SARS gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can
10 be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a cell, tissue, or organism under conditions suitable for modulating expression of the SARS target gene in the cell, tissue, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, or organism.

15 In another embodiment, the invention features a method for validating a SARS target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the SARS
20 target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi activity. The term "biological system"
25 includes, for example, a cell, tissue, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size,
30 proliferation, motility, protein expression or RNA expression or other physical or

chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Fluorescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

- 5 In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of a SARS target gene in a biological system, including, for example, in a cell, tissue, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that
10 can be used to modulate the expression of more than one SARS target gene in a biological system, including, for example, in a cell, tissue, or organism.

In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another
15 embodiment, the cell containing a siNA molecule of the invention is a human cell.

In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis
20 of the two complementary strands of the siNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety
25 than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under
30 conditions

conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example 5 under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand 10 can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as 15 described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are 20 synthesized in tandem using a cleavable linker attached to the first sequence which acts a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other 30 strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide

sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

5 In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

10 In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

15 In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

20 In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

25 In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

15 In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

20 In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

25 In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against SARS in a cell, wherein the chemical modifications do not

significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

In another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

In yet another embodiment, the invention features a method for generating siNA molecules with improved RNAi activity against SARS target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules against SARS with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct,

for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394
5 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability, comprising (a) introducing a conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved 10 bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or 15 spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically 20 modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary 25 to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or 30 improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of
5 acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a
10 terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a
15 terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in Figure 10, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

20 In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one
25 embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in Figure 10, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

30 In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting

the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In 5 another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in Figure 10 (e.g. inverted deoxyabasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating 10 RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude 15 recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for example, can result in a molecule where the 5'-end of the sense strand no longer has a 20 free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

25 In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule 30 from acting as a template or guide sequence for RNAi acitivity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have

complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide 5 sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules 10 that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and (c) introducing chemical modifications (e.g. chemical modifications as described herein 15 or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

20 In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating 25 chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be 30 present on the surface of a cell or can alternately be an intercellular receptor. Interaction

of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 2,000 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al.*, US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman *et al.*, USSN 60/402,996). Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene

expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.*, 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-
5 Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914; Allshire, 2002, *Science*, 297, 1818-
10 1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.*, 2002, *RNA*, 8, 842-850; Reinhart *et al.*, 2002, *Gene & Dev.*, 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in Figures 4-6, and
15 Tables II and III herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for
20 example wherein the double stranded region is about 19 base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the siNA is assembled from a single oligonucleotide, where the self-
25 complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having
30

self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The

5 siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a

10 portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the

15 siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiments, the siNA molecule of the invention comprises

20 separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic intercations, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise

25 nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-

30 nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of

nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however

5 have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON."

10 As used herein, the term siNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified

15 siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post-transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the

20 pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure to alter gene expression (see, for example, Verdel *et al.*, 2004, *Science*, 303, 672-676; Pal-Bhadra *et al.*, 2004, *Science*, 303, 669-672; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837;

25 Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example Figures 14-15 and Vaish *et al.*, USSN 10/727,780 filed December 3, 2003).

30 In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example Figures 16-22 and Jadhav *et al.*, USSN 60/543,480, filed February 10,

2004). The multifunctional siNA of the invention can comprise sequence targeting, for example, two regions of SARS RNA (see for example target sequences in Tables II and III) or alternately, SARS RNA and cellular RNA involved in SARS virus infection or replication. In another embodiment, a multifunctional siNA of the invention can 5 comprise sequence targeting for example both viral genes encoding RNAi inhibitory factors and viral genes encoding viral structural proteins.

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense 10 region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g., about 19, 20, 21, or 22) nucleotides) and a loop region comprising about 4 to about 8 15 (e.g., about 4, 5, 6, 7, or 8) nucleotides, and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non- 20 nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex. For example, an asymmetric duplex siNA molecule of the invention can 25 comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g. about 19, 20, 21, or 22) nucleotides) and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region.

30 By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or

activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

5 By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA
10 molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule
15 of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "gene", or "target gene", is meant, a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-
20 coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional
25 or regulatory cellular processes. Aberrant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of an organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination,
30 methylation etc.). The target gene can be a gene derived from a cell, an endogenous gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus,

which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include 5 vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts.

By "SARS" or "SARS virus" as used herein is meant the SARS virus or any protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome. The term "SARS" also includes nucleic acid molecules encoding RNA or protein(s) associated with the development and/or maintenance of SARS virus infection, 10 such as nucleic acid molecules which encode SARS RNA or polypeptides (such as polynucleotides having Genbank Accession numbers shown in Table I), including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as genes involved in SARS pathways of gene expression and/or SARS activity. Also, the term "SARS" is meant to encompass SARS viral gene products 15 and genes that modulate cellular targets for SARS virus infection, such as those described herein.

By "SARS protein" or "SARS virus protein" is meant, protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome or alternately, cellular proteins involved in SARS virus infection and/or replication.

20 By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different members of a gene family, different protein epitopes, different protein isoforms or 25 completely divergent genes, such as a cytokine and its corresponding receptors. A homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence. 30 Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%,

95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one 5 biological system or organism to another biological system or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By "sense region" is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense 10 region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By "antisense region" is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

15 By "target nucleic acid" is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free 20 energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci. USA* 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides 25 out of a total of 10 nucleotides in the first oligonucleotide being based paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and

100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

The siNA molecules of the invention represent a novel therapeutic approach to
5 treat various diseases and conditions, including SARS virus infection, acute respiratory failure, viral pneumonia, and any other indications that can respond to the level of SARS in a cell or tissue. The reduction of SARS expression and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

In one embodiment of the present invention, each sequence of a siNA molecule of
10 the invention is independently about 18 to about 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (e.g., about 17, 18, 19, 20, 21, 22 or 23). In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to
15 about 55 (e.g., about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44 (e.g., 38; 39, 40, 41, 42, 43 or 44) nucleotides in length and comprising about 16 to about 22 (e.g., about 16, 17, 18, 19, 20, 21 or 22) base pairs. Exemplary siNA molecules of the invention are shown in **Table II**. Exemplary synthetic siNA molecules of the invention are shown in **Table III** and/or **Figures 4-5**.

20 As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, e.g., specifically does not refer to a human. The cell can be present in an organism, e.g., birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (e.g., bacterial cell) or eukaryotic (e.g., mammalian or plant cell). The cell can be of somatic or germ line origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.
25

The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to
30 relevant tissues *ex vivo*, or *in vivo* through injection, infusion pump or stent, with or

without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in Tables II-III and/or Figures 4-5. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in 5 Table IV can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By 10 "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a β -D-ribo-furanose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more 15 nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as 20 analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

25 The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term "thiophosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and

- 5 W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl
10 and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or
15 C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein (e.g., cancers and other proliferative conditions). For example, to treat a particular disease or condition, the siNA molecules can be administered to a subject or can be
20 administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic agents to treat a disease or condition. Non-limiting examples of other therapeutic agents that can be readily combined with a siNA molecule of the invention are enzymatic nucleic acid molecules, allosteric nucleic acid molecules, antisense, decoy, or aptamer nucleic acid molecules, antibodies such as monoclonal antibodies, small molecules, and other organic and/or inorganic compounds including metals, salts and ions.
25

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector 5 can also contain sequence(s) encoding a single nucleic acid molecule that is self-complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online 10 publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by 15 a Genbank Accession numbers, for example Genbank Accession Nos. shown in Table I.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target 20 RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as 25 described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by 30 administration to target cells ex-planted from a subject followed by reintroduction into

the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

5 Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are 10 synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group, 15 remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl-on purification method wherein only duplexes/oligonucleotides with the terminal protecting 20 group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a 25 simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in

turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N)). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all

pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified 5 internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

Figure 4C: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and 10 wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'- fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'- terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally 15 complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N)-nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as 20 described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4D: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and 25 wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the 30 target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are

2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown
5 as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4E: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,
10 deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are
15 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

20 Figure 4F: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and
25 wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro
30 modified nucleotides and all purine nucleotides that may be present are 2'-deoxy nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,

deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of 5 constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glycerol moiety (L) is present at the 3'-end of the antisense strand for any construct shown in Figure 4 A-F, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA sequences of the invention. A-F applies the chemical modifications described in Figure 10 4A-F to a SARS virus siNA sequence. Such chemical modifications can be applied to any SARS sequence and/or SARS polymorphism sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base 15 pairs; however, different embodiments of the invention include any number of base pairs described herein. Bracketed regions represent nucleotide overhangs, for example comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as 20 a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the 25 active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

Figure 7A: A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence 5 of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

Figure 7B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a SARS target sequence and having self-complementary sense and antisense regions.

Figure 7C: The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology*, 29, 505-508.

Figure 8A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

Figure 8A: A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence 20 followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

Figure 8B: The synthetic construct is then extended by DNA polymerase to 25 generate a hairpin structure having self-complementary sequence.

Figure 8C: The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense

strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, 5 such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

10 **Figure 9B&C:** (Figure 9B) The sequences are pooled and are inserted into vectors such that (Figure 9C) transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

15 **Figure 9E:** The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including (1) [3'-3']-inverted deoxyribose; (2) deoxyribonucleotide; (3) [5'-3']-20 3'-deoxyribonucleotide; (4) [5'-3']-ribonucleotide; (5) [5'-3']-3'-O-methyl ribonucleotide; (6) 3'-glyceryl; (7) [3'-5']-3'-deoxyribonucleotide; (8) [3'-3']-deoxyribonucleotide; (9) [5'-2']-deoxyribonucleotide; and (10) [5'-3']-dideoxyribonucleotide. In addition to modified 25 and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

Figure 11 shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-mofications, 5 base modifications, backbone modifications, terminal cap modifications etc). The modified construct is tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a 10 particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

Figure 12 shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

15 Figure 13 shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

Figure 14A shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palindrome and/or repeat nucleic acid sequences that are identified in a target nucleic acid sequence. (i) A palindrome or repeat sequence 20 is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palindrome sequence. (iii) An inverse repeat sequence of the non-palindrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO molecule comprising sequence complementary to the nucleic acid 25 target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. Figure 14B shows a non-limiting representative example of a duplex forming oligonucleotide sequence. Figure 14C shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. Figure 14D shows a non-limiting example of the self assembly schematic of a 30 representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

Figure 15 shows a non-limiting example of the design of self complementary DFO constructs utilizing palindrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palindrome/repeat sequences allow the
5 design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palindrome (shown as XYXYXY in
10 the Figure). An inverse repeat of the non-palindrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

Figure 16 shows non-limiting examples of multifunctional siNA molecules of the
15 invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. Figure 16A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid
20 sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. Figure
25 16B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA.
30 The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 17A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 17B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 16**.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 18A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and

wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have

5 complementarity to the target nucleic acid sequences. Figure 18B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each

10 polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

15 Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA

20 constructs that can mediate RNA interference against differing target nucleic acid sequences. Figure 19A shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second

25 complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not

30 have complementarity to the target nucleic acid sequences. Figure 19B shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a

second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 18**.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent biologic pathway that is implicated in the maintenance of progression of disease. Each strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid sequences within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target region. These

design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide 5 positions as is known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Mechanism of Action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA 10 and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or "improved RNAi activity" is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of 15 these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA and/or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability 20 of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*, 25 1998, *Nature*, 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999,

- Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response though a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.
- 10 The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from Dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes.
- 15 Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded
- 20 RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably through cellular mechanisms that regulate chromatin structure and thereby
- 25 prevent transcription of target gene sequences (see for example Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237). As such, siRNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein
- 30 such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA.

5 Elbashir *et al.*, 2001, *Nature*, 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown

10 that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi

15 activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*; 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA

20 (Nykanen *et al.*, 2001, *Cell*, 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using

25 automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; e.g., individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous

30 delivery. The simple structure of these molecules increases the ability of the nucleic acid

to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (e.g., certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol. Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μ mol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μ mol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μ L of 0.11 M = 6.6 μ mol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μ L of 0.25 M = 15 μ mol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μ L of 0.11 M = 4.4 μ mol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μ L of 0.25 M = 10 μ mol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% N-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained

from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the 5 polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, 10 containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and 15 makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides. 20 Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 μL of 0.11 M = 13.2 μmol) of alkylsilyl (ribo) 25 protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 μL of 0.25 M = 30 μmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. 30 synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems,

- Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson
- 5 Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide 0.05 M in acetonitrile) is used.
- 10 Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of
- 15 EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 μL of a solution of 1.5 mL N-methylpyrrolidinone, 750 μL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C.
- 20 After 1.5 h, the oligomer is quenched with 1.5 M NH₄HCO₃.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is

25 heated at 65 °C for 15 minutes. The sample is cooled at -20 °C and then quenched with 1.5 M NH₄HCO₃.

For purification of the trityl-on oligomers, the quenched NH₄HCO₃ solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is

30 detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with

water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that

- 5 the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No.

- 10 WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection.

- The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are
15 synthesized as a single contiguous oligonucleotide fragment or strand-separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms
20 such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

- A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment
25 includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can

be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al.*, *supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

In another aspect of the invention, siNA molecules of the invention are expressed
5 from transcription units inserted into DNA or RNA vectors. The recombinant vectors can
be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed
based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus.
The recombinant vectors capable of expressing the siNA molecules can be delivered as
described herein, and persist in target cells. Alternatively, viral vectors can be used that
10 provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar
and/or phosphate) can prevent their degradation by serum ribonucleases, which can
increase their potency (see e.g., Eckstein *et al.*, International Publication No. WO
15 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314;
Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*,
International Publication No. WO 93/15187; and Rossi *et al.*, International Publication
No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.*, U.S. Pat. No. 6,300,074;
and Burgin *et al.*, *supra*; all of which are incorporated by reference herein). All of the
20 above references describe various chemical modifications that can be made to the base,
phosphate and/or sugar moieties of the nucleic acid molecules described herein.
Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid
molecules to shorten oligonucleotide synthesis times and reduce chemical requirements
are desired.

25 There are several examples in the art describing sugar, base and phosphate
modifications that can be introduced into nucleic acid molecules with significant
enhancement in their nuclease stability and efficacy. For example, oligonucleotides are
modified to enhance stability and/or enhance biological activity by modification with
nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-O-
30 allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992,

TIBS, 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al.*, *International Publication* PCT No. WO 92/07065; Perrault *et al.* *Nature*, 1990, 344, 565-568; Pieken *et al.* *Science*, 1991, 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman *et al.* *International Publication* PCT No. WO 93/15187; Sproat, U.S. Pat. No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, International PCT publication No. WO 97/26270; Beigelman *et al.*, U.S. Pat. No. 5,716,824; Usman *et al.*, U.S. Pat. No. 5,627,053; Woolf *et al.*, International PCT Publication No. WO 98/13526; Thompson *et al.*, USSN 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Eamshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the

goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA 5 and DNA (Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more 10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in 15 substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 20 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to 25 facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel 30 conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic

- acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers.
- 5 These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker
- 10 molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the

15 invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino,

20 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or

25 phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or

30 molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in

- combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.
- 10 The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.
- 15 Therapeutic nucleic acid molecules (*e.g.*, siNA molecules) delivered exogenously optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify 20 nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.

25 Use of the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (*e.g.*, multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with 30 combinations of molecules, including different motifs and/or other chemical or

biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

5 In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'- cap structure, for example on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.*, U.S. Pat. No. 10 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'-methylene nucleotide; 1-(beta-D-erythofuranosyl) nucleotide, 4'-thio nucleotide; carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic 15 moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging 20 methylphosphonate moiety.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, 25 inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythofuranosyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminohexyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; 30 phosphorodithioate; *threo*-pentofuranosyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide

moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer,
5 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not
10 contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to
15 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons.
20 More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂, halogen, N(CH₃)₂, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond,
25 including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The 5 preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl 10 groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. 15 An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the 20 sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*, all are hereby incorporated by reference 25 herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 30 5-alkylcytidines (e.g., 5-methylcytidine), 5-alkyluridines (e.g., ribothymidine), 5-halouridine (e.g., 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (e.g. 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090;

Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, 5 phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amide carbamate, carboxymethyl, acetamide, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and 10 Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

15 By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of β-D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII 20 and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH₂ or 2'-O- NH₂, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.*, U.S. Pat. No. 6,248,878, which are both incorporated by 25 reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, e.g., to

enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Administration of Nucleic Acid Molecules

A siRNA molecule of the invention can be adapted for use to treat for example SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue, alone or in combination with other therapies. For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.*, 1999, *Mol. Membr. Biol.*, 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.*, 137, 165-192; and Lee *et al.*, 2000, *ACS Symp. Ser.*, 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.*, U.S. Pat. No. 6,395,713 and Sullivan *et al.*, PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang *et al.*, International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump.

In one embodiment, the nucleic acid molecules or the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation
5 administered by an inhalation device or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. Solid particulate compositions containing respirable dry particles of micronized nucleic acid compositions can be prepared by grinding dried or lyophilized nucleic acid compositions, and then passing the micronized composition through, for example, a 400 mesh screen to break up or separate
10 out large agglomerates. A solid particulate composition comprising the nucleic acid compositions of the invention can optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which can be blended with the nucleic acid compound in any suitable ratio, such as a 1 to 1 ratio by weight.

15 Aerosols of liquid particles comprising a nucleic acid composition of the invention can be produced by any suitable means, such as with a nebulizer (see for example US 4,501,729). Nebulizers are commercially available devices which transform solutions or suspensions of an active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi
20 orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride or other suitable salts. Optional additives
25 include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, anti-oxidants, flavorings, volatile oils, buffering agents and emulsifiers and other formulation surfactants. The aerosols of solid particles comprising the active composition and surfactant can likewise be produced with any solid particulate aerosol generator. Aerosol generators for administering solid particulate therapeutics to a subject
30 produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a therapeutic composition at a rate

suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which can be delivered by means of an insufflator. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the 5 treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as 10 lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted 15 to deliver a metered volume to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, emulsifiers and other formulation surfactants, such as oleic acid or 20 sorbitan trioleate, anti-oxidants and suitable flavoring agents. Other methods for pulmonary delivery are described in, for example US Patent Application No. 20040037780, and US Patent Nos. 6,592,904; 6,582,728; 6,565,885.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Application 25 Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

30 Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and

the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable administration, and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the

association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells producing excess repeat expansion genes.

5 By "pharmaceutically acceptable formulation" is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85);,
10 biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery (Emerich, DF *et al.*, 1999, *Cell Transplant*, 8, 47-58); and loaded nanoparticles, such as those made of polybutylcyanoacrylate. Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et*
15 *al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596; Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et.al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer a method for increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al.* *Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al.*, *Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al.*, *Science* 1995, 267, 1275-1276; Oku *et al.*, 1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al.*, *J. Biol. Chem.* 1995, 42, 24864-24870; Choi *et al.*, International PCT

Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid 5 accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, 10 for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

15 A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence; or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent 20 medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage 25 unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a 30 pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically

acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard 5 or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring 10 agents or preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium 15 carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay 20 disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

25 Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example, 30 lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain

aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene 5 sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a 10 vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

15 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring 20 agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, 25 lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, 30 propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a

demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above.

5 The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any

10 bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either 20 be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be 25 combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age, 30 body weight, general health, sex, diet, time of administration, route of administration,

and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and
5 drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall
10 therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example,
15 triantennary structures are bound with greater affinity than biantennary or monoantennary chains (Baenziger and Fiete, 1980, *Cell*, 22, 611-620; Connolly *et al.*, 1982, *J. Biol. Chem.*, 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect"
20 has also been described for the binding and uptake of mannose-terminating glycoproteins or glycoconjugates (Ponpipom *et al.*, 1981, *J. Med. Chem.*, 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach
25 to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavailability,
30

pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.*, USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.*, USSN 10/151,116, filed May 17, 2002. In one embodiment,
5 nucleic acid molecules of the invention are complexed with or covalently attached to nanoparticles, such as Hepatitis B virus S, M, or L envelope proteins (see for example Yamado *et al.*, 2003, *Nature Biotechnology*, 21, 885). In one embodiment, nucleic acid molecules of the invention are delivered with specificity for human tumor cells, specifically non-apoptotic human tumor cells including for example T-cells, hepatocytes,
10 breast carcinoma cells, ovarian carcinoma cells, melanoma cells, intestinal epithelial cells, prostate cells, testicular cells, non-small cell lung cancers, small cell lung cancers, etc.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (e.g., Izant and Weintraub, 1985, *Science*, 229, 15 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci. USA* 83, 399; Scanlon *et al.*, 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science*, 247, 20 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 25 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510)
30 inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited

to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, 5 and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by 10 administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression 15 vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee 20 *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (e.g., eukaryotic pol I, II or III initiation region); b) a transcription termination region (e.g., eukaryotic pol I, II or III termination region); and 25 c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention, wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the 30 invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature 5 of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. 10 Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO 15 J.*, 11, 4411-8; Lisziewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A.*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells 20 (Thompson *et al.*, *supra*; Couture and Stinchcomb, 1996, *supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, 25 viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, *supra*).

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner 30 that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule,

wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

SARS virus biology and biochemistry

The following discussion is adapted from the report, "Preliminary Clinical Description of Severe Acute Respiratory Syndrome", World Health Organization, Geneva, Switzerland, available at the Centers for Disease Control and Prevention website.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS

global outbreak of 2003 was contained. According to the World Health Organization (WHO), a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak. Of these, 774 died.

The incubation period for SARS is typically 2--7 days; however, isolated reports
5 have suggested an incubation period as long as 10 days. The illness begins generally with a prodrome of fever ($>100.4^{\circ}\text{F}$ [$>38.0^{\circ}\text{C}$]). Fever often is high, sometimes is associated with chills and rigors, and might be accompanied by other symptoms, including headache, malaise, and myalgia. At the onset of illness, some persons have mild respiratory symptoms. Typically, rash and neurologic or gastrointestinal findings are
10 absent; however, some patients have reported diarrhea during the febrile prodrome.

After 3--7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea, which might be accompanied by or progress to hypoxemia. In 10%--20% of cases, the respiratory illness is severe enough to require intubation and mechanical ventilation. Death may result from progressive respiratory
15 failure due to alveolar damage. The case-fatality rate among persons with illness meeting the current WHO case definition of SARS is approximately 3%.

Chest radiographs might be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal interstitial infiltrates progressing to more generalized,
20 patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS also have shown areas of consolidation.

Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts have generally been normal or decreased. At the peak of the respiratory illness, approximately 50% of patients have leukopenia and
25 thrombocytopenia or low-normal platelet counts (50,000--150,000/ μL). Early in the respiratory phase, elevated creatine phosphokinase levels (as high as 3,000 IU/L) and hepatic transaminases (two to six times the upper limits of normal) have been noted. In the majority of patients, renal function has remained normal.

The severity of illness might be highly variable, ranging from mild illness to death. Although a few close contacts of patients with SARS have developed a similar illness, the majority have remained well. Some close contacts have reported a mild, febrile illness without respiratory signs or symptoms, suggesting the illness might not always 5 progress to the respiratory phase.

Treatment regimens have included several antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy also has included antiviral agents such as oseltamivir or ribavirin. Steroids have also been administered orally or intravenously to patients in combination with ribavirin and other antimicrobials. 10

At present, the most efficacious treatment regimen, if any, is unknown.

The causative agent of SARS appears to be a novel coronavirus that was isolated from patients who met the case definition of SARS (see Ksiazek et al., 2003, New England Journal of Medicine, 10.1056/NEJMoa030781. Indirect fluorescent antibody tests and enzyme-linked immunosorbent assays made with the new coronavirus isolate 15 have been used to demonstrate a virus-specific serologic response. Amplification of short regions of the polymerase gene, (the most strongly conserved part of the Coronavirus genome) by reverse transcriptase polymerase chain reaction (RT-PCR) and nucleotide sequencing revealed that the SARS virus is a novel Coronavirus which has not previously been present in human populations. This conclusion is confirmed by 20 serological (antigenic) investigations. The sequence of the SARS associated coronavirus was recently made available through the CDC.

Viral entry into cells occurs via endocytosis and membrane fusion. Replication occurs in the cytoplasm. Initially, the 5' 20kb of the (+)sense genome is translated to produce a viral polymerase, which then produces a full-length (-)sense strand. This is 25 used as a template to produce mRNA as a nested set of transcripts, all with an identical 5' non-translated leader sequence of 72nt and coincident 3' polyadenylated ends. Each mRNA is monocistronic, the genes at the 5' end being translated from the longest mRNA. These unusual cytoplasmic structures are produced not by splicing but by the polymerase during transcription. Between each of the genes there is a repeated intergenic 30 sequence - UCUAAAC - which interacts with the transcriptase plus cellular factors to splice the leader sequence onto the start of each ORF. Viral assembly occurs by budding

into the golgi apparatus, and viral particles are transported to the surface of the cell and are subsequently released.

The SARS virus can be grown in Vero cells (a fibroblast cell line isolated in 1962 from a primate). This is a novel property for human coronaviruses which usually cannot
5 be cultivated. In these cells, virus infection results in a cytopathic effect, and budding of Coronavirus-like particles from the endoplasmic reticulum within infected cells.

Detection of the SARS virus can be accomplished with serological testing and molecular diagnostic procedures. Serological testing for anti-Coronavirus antibodies consists of indirect fluorescent antibody testing and enzyme-linked immunosorbent
10 assays (ELISA) which detect antibodies against the virus produced in response to infection. Molecular testing consists of reverse transcriptase-polymerase chain reaction (RT-PCR) tests specific for the RNA from the novel Coronavirus.

The use of small interfering nucleic acid molecules targeting SARS genes therefore provides a class of novel therapeutic agents that can be used in the treatment and
15 diagnosis of SARS virus infection, acute respiratory failure, viral pneumonia, or any other disease or condition that responds to modulation of SARS genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

20 Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high
25 throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-O-DMT) group remains intact (trityl on synthesis), the

- oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.
- 10 Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see Figure 1) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such
- 15 as Bromotripyrrolidinophosphoniumhexafluorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M NH₄H₂CO₃.
- 20 Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV H₂O, and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV H₂O or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The
- 25 column is then washed, for example with 1 CV H₂O followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with H₂O followed by 1 CV 1M NaCl and additional
- 30 H₂O. The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA construct only shows a single peak. Testing of the purified siNA construct using a luciferase reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

10 Example 2: Identification of potential siNA target sites in any RNA sequence

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be used. High throughput screening assays can be developed for screening siNA molecules

using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

The following non-limiting steps can be used to carry out the selection of siNAs
5 targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial sequence analysis programs such as Oligo, MacVector, or the GCG 10 Wisconsin Package can be employed as well.
2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can identify subsequences that are unique to a target sequence, such as a mutant target 15 sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.
- 20 3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene 25 but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.
5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.
10. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.
15. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.
20. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see Tables II and III). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.
25. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see for example Reynolds *et al.*, 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Uti-Tei *et al.*, 2004, *Nucleic Acids Research*, 32, doi:10.1093/nar/gkh247.

5 In an alternate approach, a pool of siNA constructs specific to a SARS target sequence is used to screen for target sites in cells expressing SARS RNA, such as VERO cells and/or FRhk-4 cells. The general strategy used in this approach is shown in Figure 9. A non-limiting example of such is a pool comprising sequences having SEQ ID NOS: 1-3392. Cells expressing SARS (e.g., VERO cells and/or FRhk-4 cells) are transfected
10 with the pool of siNA constructs and cells that demonstrate a phenotype associated with SARS inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example Figure 7 and Figure 8). The siNA from cells demonstrating a positive phenotypic change (e.g., decreased proliferation, decreased SARS mRNA levels or decreased SARS protein
15 expression), are sequenced to determine the most suitable target site(s) within the target SARS RNA sequence.

Example 4: SARS targeted siNA design

siNA target sites were chosen by analyzing sequences of the SARS RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of
25 the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example
30 those RNA sequences corresponding to the any gene transcript.

Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration *in vivo* and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods 5 described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantify RNAi activity. Synthetic siNA constructs that 10 possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example Figure 11).

15 **Example 5: Chemical Synthesis and Purification of siNA**

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using 20 methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can be synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 25 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.*, US Patent Nos. 6,111,086; 6,008,400; 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphosphoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine, 30

N4 acetyl cytidine, and N2-isobutyryl guanosine). Alternately, 2'-O-Silyl Ethers can be used in conjunction with acid-labile 2'-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra*. Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl 5 protection as described by Usman *et al.*, US Patent 5,631,360, incorporated by reference herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3' - to 5'- direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3'-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or 10 polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5'-end of the first nucleoside. The support is then washed and any unreacted 5'-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5'-acetyl moieties. The trivalent phosphorus linkage is 15 then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition cycle, the 5'-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, 20 for example by using differing coupling times, differing reagent/phosphoramidite concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Deprotection and purification of the siNA can be performed as is generally 25 described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra*, incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides 30 can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-

2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

Example 6: RNAi *in vitro* assay to assess siNA activity

- 5 An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting SARS RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with SARS target RNA. A Drosophila extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target
- 10 RNA is generated via *in vitro* transcription from an appropriate SARS expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C , then diluted in
- 15 lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide. The Drosophila lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the
- 20 supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug.ml creatine phosphokinase, 100 um GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid.
- 25 The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in
- 30 which siNA is omitted from the reaction.

- Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [alpha-³²P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'-³²P-end labeled using T4 polynucleotide kinase enzyme.
- 5 Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by PHOSPHOR IMAGER® (autoradiography) quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.
- 10 In one embodiment, this assay is used to determine target sites the SARS RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the SARS RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.
- 15 Example 7: Nucleic acid inhibition of SARS target RNA *in vitro*
- siNA molecules targeted to the human SARS RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target sequences and the nucleotide location within the SARS RNA are given in Table II and III.
- 20 Two formats are used to test the efficacy of siNAs targeting SARS. First, the reagents are tested in cell culture using, for example, VERO cells and/or FRhk-4 cells, to determine the extent of RNA and protein inhibition. siNA reagents (e.g.; see Tables II and III) are selected against the SARS target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example,
- 25 VERO cells and/or FRhk-4 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (eg., ABI 7700 TAQMAN®). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen
- 30 for the target and optimization performed. After an optimal transfection agent

concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

Delivery of siNA to Cells

5 Cells (e.g., VERO cells and/or FRhk-4 cells infected with the SARS virus) are seeded, for example, at 1×10^5 cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration 2 μ g/ml) are complexed in EGM basal media (Bio Whittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the
10 complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at 1×10^3 in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at
15 room temperature. Uptake of siNA is visualized using a fluorescent microscope.

TAQMAN® (real-time PCR monitoring of amplification) and Lightcycler quantification of mRNA

Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For
20 TAQMAN® analysis (real-time PCR monitoring of amplification), dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50 μ l reactions consisting of 10 μ l total RNA, 100 nM forward primer, 900 nM reverse primer,
25 100 nM probe, 1X TAQMAN® PCR reaction buffer (PE-Applied Biosystems), 5.5 mM MgCl₂, 300 μ M each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AMPLITAQ GOLD® (DNA polymerase) (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C, 10 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C
30 and 1 minute at 60°C. Quantitation of mRNA levels is determined relative to standards

generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/rxn) and normalizing to β -actin or GAPDH mRNA in parallel TAQMAN® reactions (real-time PCR monitoring of amplification). For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcyler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research*, 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hours at 4°C. Following washes, the secondary antibody is applied, for example (1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

Example 8: RNAi mediated inhibition of SARS RNA expression

siNA constructs (e.g., siNA constructs shown in Table III) are tested for efficacy in reducing SARS RNA expression in, for example, VERO cells and/or FRhk-4 cells. Cells are plated approximately 24h before transfection in 96-well plates at 5,000-7,500 cells/well, 100 μ l/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 μ l/well and incubated for 20 minutes at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150 μ l. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the

continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene
5 and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

In a non-limiting example, a siNA construct comprising ribonucleotides and 3'-
10 terminal dithymidine caps is assayed along with a chemically modified siNA construct comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides and purine ribonucleotides in which the sense strand of the siNA is further modified with 5' and 3'-terminal inverted deoxyabasic caps and the antisense strand comprises a 3'-terminal phosphorothioate internucleotide linkage. Additional stabilization chemistries as described in Table IV are
15 similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

Example 9: Animal Models

Evaluating the efficacy of anti-SARS agents in animal models is an important prerequisite to human clinical trials. Byron *et al.*, 2003, *Nature*, 425, 915, describe ferret and feline animal models of SARS virus infection. Haagmans *et al.*, 2004, *Nature Medicine*, 10, 290-293, describe the use of pegylated interferon-alpha in protecting type 1 pneumocytes against SARS coronavirus infection in macaques. Gao *et al.*, 2003, 20
25 *Lancet*, 362, 1895-6, describe the use of a SARS virus vaccine in monkeys. All of these models can be adapted for use for pre-clinical evaluation of the efficacy of nucleic acid compositions of the invention in modulating SARS virus gene expression toward therapeutic use.

Example 10: Indications

The present body of knowledge in SARS research indicates the need for methods to assay SARS activity and for compounds that can regulate SARS expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related of SARS levels. In addition, the nucleic acid molecules can be used to treat disease state related to SARS levels.

Particular degenerative and disease states that can be associated with SARS expression modulation include, but are not limited to, SARS virus infection, liver failure, hepatocellular carcinoma, cirrhosis, and/or other disease states associated with SARS virus infection.

Immunomodulators, steroids, and anti-vrial compounds are non-limiting examples of pharmaceutical agents that can be combined with or used in conjunction with the nucleic acid molecules (e.g. siNA molecules) of the instant invention. The use of ribavirin and oseltamivir are non-limiting examples of chemotherapeutic agents that can be combined with or used in conjunction with the nucleic acid molecules (e.g. siNA molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (e.g. siNA molecules) and are hence within the scope of the instant invention.

20 Example 11: Interferons

Interferons represent a non-limiting example of a class of compounds that can be used in conjunction with the siNA molecules of the invention for treating the diseases and/or conditions described herein. Type I interferons (IFN) are a class of natural cytokines that includes a family of greater than 25 IFN- α (Pesta, 1986, *Methods Enzymol.* 119, 3-14) as well as IFN- β , and IFN- ω . Although evolutionarily derived from the same gene (Diaz *et al.*, 1994, *Genomics* 22, 540-552), there are many differences in the primary sequence of these molecules, implying an evolutionary divergence in biologic activity. All type I IFN share a common pattern of biologic effects that begin with binding of the IFN to the cell surface receptor (Pfeffer & Strulovici, 1992, 25 Transmembrane secondary messengers for IFN- α/β . In: *Interferon. Principles and*

Medical Applications., S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tyring, eds. 151-160). Binding is followed by activation of tyrosine kinases, including the Janus tyrosine kinases and the STAT proteins, which leads to the production of several IFN-stimulated gene products (Johnson *et al.*, 1994, *Sci. Am.* 270, 68-75). The IFN-stimulated gene products are responsible for the pleotropic biologic effects of type I IFN, including antiviral, antiproliferative, and immunomodulatory effects, cytokine induction, and HLA class I and class II regulation (Pestka *et al.*, 1987, *Annu. Rev. Biochem.* 56, 727). Examples of IFN-stimulated gene products include 2'-5'-oligoadenylate synthetase (2'-OAS), β_2 -microglobulin, neopterin, p68 kinases, and the Mx protein (Chebath & Revel, 1992, The 2'-5' A system: 2'-5' A synthetase, isospecies and functions. In: *Interferon. Principles and Medical Applications*, S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Jr. Fleischmann, T.K. Jr Hughes, G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tyring, eds., pp. 225-236; Samuel, 1992, The RNA-dependent P1/eIF-2 α protein kinase. In: 15 *Interferon. Principles and Medical Applications*. S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tyring, eds. 237-250; Horisberger, 1992, MX protein: function and Mechanism of Action. In: *Interferon. Principles and Medical Applications*. S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, 20 D.W. Niesel, G.H. Stanton, and S.K. Tyring, eds. 215-224). Although all type I IFN have similar biologic effects, not all the activities are shared by each type I IFN, and in many cases, the extent of activity varies quite substantially for each IFN subtype (Fish *et al.*, 1989, *J. Interferon Res.* 9, 97-114; Ozes *et al.*, 1992, *J. Interferon Res.* 12, 55-59). More specifically, investigations into the properties of different subtypes of IFN- α and 25 molecular hybrids of IFN- α have shown differences in pharmacologic properties (Rubinstein, 1987, *J. Interferon Res.* 7, 545-551). These pharmacologic differences can arise from as few as three amino acid residue changes (Lee *et al.*, 1982, *Cancer Res.* 42, 1312-1316).

Eighty-five to 166 amino acids are conserved in the known IFN- α subtypes. 30 Excluding the IFN- α pseudogenes, there are approximately 25 known distinct IFN- α subtypes. Pairwise comparisons of these nonallelic subtypes show primary sequence

differences ranging from 2% to 23%. In addition to the naturally occurring IFNs, a non-natural recombinant type I interferon known as consensus interferon (CIFN) has been synthesized as a therapeutic compound (Tong *et al.*, 1997, *Hepatology* 26, 747-754).

Interferon is currently in use for at least 12 different indications, including
5 infectious and autoimmune diseases and cancer (Borden, 1992, *N. Engl. J. Med.* 326,
1491-1492). For autoimmune diseases, IFN has been utilized for treatment of
rheumatoid arthritis, multiple sclerosis, and Crohn's disease. For treatment of cancer,
IFN has been used alone or in combination with a number of different compounds.
10 Specific types of cancers for which IFN has been used include squamous cell
carcinomas, melanomas, hypernephromas, hemangiomas, hairy cell leukemia, and
Kaposi's sarcoma. In the treatment of infectious diseases, IFNs increase the phagocytic
activity of macrophages and cytotoxicity of lymphocytes and inhibits the propagation of
cellular pathogens. Specific indications for which IFN has been used as treatment
include hepatitis B, human papillomavirus types 6 and 11 (i.e. genital warts) (Leventhal
15 *et al.*, 1991, *N Engl J Med* 325, 613-617), chronic granulomatous disease, and SARS
virus.

Pegylated interferons, i.e., interferons conjugated with polyethylene glycol (PEG),
have demonstrated improved characteristics over interferon. Advantages incurred by
PEG conjugation can include an improved pharmacokinetic profile compared to
20 interferons lacking PEG, thus imparting more convenient dosing regimes, improved
tolerance, and improved antiviral efficacy. Such improvements have been demonstrated
in clinical studies of both polyethylene glycol interferon alfa-2a (PEGASYS, Roche) and
polyethylene glycol interferon alfa-2b (VIRAFERON PEG, PEG-INTRON,
Enzon/Schering Plough).

25 siNA molecules in combination with interferons and polyethylene glycol
interferons have the potential to improve the effectiveness of treatment of SARS or any
of the other indications discussed above. siNA molecules targeting RNAs associated
with SARS virus infection can be used individually or in combination with other
therapies such as interferons and polyethylene glycol interferons and to achieve
30 enhanced efficacy.

Example 12: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls,

synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and 5 mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain 10 insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the 15 initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each 20 reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as 25 limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the 30 scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches

one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses
5 mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the
10 absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of
15 such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to
20 by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of
Markush groups or other grouping of alternatives, those skilled in the art will recognize
that the invention is also thereby described in terms of any individual member or
25 subgroup of members of the Markush group or other group.

Table I: SARS virus Accession Numbers

5 LOCUS NC_004718 29736 bp ss-RNA linear VRL 15-APR-2003
DEFINITION SARS coronavirus, complete genome.
ACCESSION NC_004718

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Table II: SARS siNA and Target Sequences

SARS CoV NC_004718		Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID	UPos	Upper seq	Seq ID	UPos	Upper seq	Seq ID	UPos	Upper seq
Pos	Seq																					
3	ACCCAGGAAAGCCAACCA	1	3	ACCCAGGAAAGCCAACCA	1	21	UCUACAGGCUUUUUCUGGGU	1652														
21	AACCUCGGAUCGUAGA	2	21	AACCUCGGAUCGUAGA	2	39	UCUACAGGCUUUUUCUGGGU	1653														
39	AUCUGUUCUICUAAACGAAC	3	39	AUCUGUUCUICUAAACGAAC	3	57	GUUCGGUUUAGAAGACAGAU	1654														
57	CUUAAAUAUCUGUGUAGCU	4	57	CUUAAAUAUCUGUGUAGCU	4	75	AGCUACACAGAUUUUUAAAG	1655														
75	UGUCCGCUCCGCUAUGC	5	75	UGUCCGCUCCGCUAUGC	5	93	GGCAUGCGCAGGGCACAGA	1656														
93	CUAGUGCACCUACCGAGUA	6	93	CUAGUGCACCUACCGAGUA	6	111	UACUGGUAGGGUGGCACUAG	1657														
111	AUAAAACAUAUAUAUUUU	7	111	AUAAAACAUAUAUAUUUU	7	129	AAAAAUUUAUAUAUUAUUUU	1658														
129	UACUGGUAGGGUGACAAGAA	8	129	UACUGGUAGGGUGACAAGAA	8	147	UUUCUUGGUACACGACAGUA	1659														
147	ACGAGUAACUCGUCUCCUCU	9	147	ACGAGUAACUCGUCUCCUCU	9	165	AGAGGGACGAGGUACUCGU	1660														
165	UCUGGCGAGCUACGUACGG	10	165	UCUGGCGAGCUACGUACGG	10	183	CCGUAAAGCAGGUUCUGAGAA	1661														
183	GUUCUGGUCCGGGUUGUAGGU	11	183	GUUCUGGUCCGGGUUGUAGGU	11	201	ACUCCACACGACGAAAC	1662														
201	UCGAUCAUCAUCGCAUACUA	12	201	UCGAUCAUCAUCGCAUACUA	12	219	UAGGUAGGGUGAGAUGAUCGA	1663														
219	AGGUUUCGGUCCGGUGUGA	13	219	AGGUUUCGGUCCGGUGUGA	13	237	UCACACCGGGAGAAACCU	1664														
237	ACGAAAAGGUAGAUGGAG	14	237	ACGAAAAGGUAGAUGGAG	14	255	CUCCAUCUACUUACUUUCGGU	1665														
255	GAAGCCUUCGUUCUUGGUUC	15	255	GAAGCCUUCGUUCUUGGUUC	15	273	GACACCAAGAACAGGUUC	1666														
273	CAACGAGAAAACACACGUC	16	273	CAACGAGAAAACACACGUC	16	291	GACGGUGGUUUUUCUGUUG	1667														
291	CCAACUCAGGUUUGCCUGUC	17	291	CCAACUCAGGUUUGCCUGUC	17	309	GACGGGAAACUGAGUUGGG	1668														
309	CCUUCGGGUAGAGACGUG	18	309	CCUUCGGGUAGAGACGUG	18	327	CACGCCUCUACGUACUAGG	1669														
327	GUCAUGGGCGGUCCGUUCGG	19	327	GUCAUGGGCGGUCCGUUCGG	19	345	CCCCGAAGCAGCCUUCUCC	1670														
345	GGACUCUGGUAGAGGCC	20	345	GGACUCUGGUAGAGGCC	20	363	GGCCUCUUCUACAGGUCC	1671														
363	CCUAUCGGAGGGCACGUGA	21	363	CCUAUCGGAGGGCACGUGA	21	381	UUCACGGCCUCCGAUAGGG	1672														
381	ACACCUAAAAAUGGCAUC	22	381	ACACCUAAAAAUGGCAUC	22	399	AGUGCCAUUUUUGGGUGU	1673														
399	UUGGGGUUCUAGUAGCUG	23	399	UUGGGGUUCUAGUAGCUG	23	417	CACGCCUCUACGCUUUCGCC	1674														
417	GGAAAAAAAGGCCGUACGCC	24	417	GGAAAAAAAGGCCGUACGCC	24	435	GGGGAGGUACGGGUACGG	1675														
435	CCAGCUUAGAACAGCCCUC	25	435	CCAGCUUAGAACAGCCCUC	25	453	AUAGGGCGUUCUCAAGCGU	1676														
453	UGUGGUUCAUUAACGUUC	26	453	UGUGGUUCAUUAACGUUC	26	471	AGAACGUUUAAGGAACACA	1677														
471	UGAUGCCUUAAGGCAAU	27	471	UGAUGCCUUAAGGCAAU	27	489	AUUGGGGUUAGGGCUACUA	1678														
489	UCACGGCCACAAAGGCU	28	489	UCACGGCCACAAAGGCU	28	507	AACGCCUCUACGGGUACUCA	1679														
507	UGAGCCUGGUUGGAGAAAG	29	507	UGAGCCUGGUUGGAGAAAG	29	525	CAUUCUCGCAACCCAGCUCA	1680														
525	GAACGGCAUUCAGUACGGU	30	525	GAACGGCAUUCAGUACGGU	30	543	ACCGGUACUAGAAGCCGUCC	1681														
543	UCGUAGGGGUAAACACUG	31	543	UCGUAGGGGUAAACACUG	31	561	CAGGUUAUACGGCUACGA	1682														
561	GGAGGUACUUCGGCCACAU	32	561	GGAGGUACUUCGGCCACAU	32	579	AUGUGGGACGUACUCC	1683														
579	UGUGGGCGAAAACCCCAAU	33	579	UGUGGGCGAAAACCCCAAU	33	597	AAUUGGGGUUUGGCCACAA	1684														
597	UGCAUACGGCAAUUGUUCU	34	597	UGCAUACGGCAAUUGUUCU	34	615	AAGAACAUUUGGGUAUGCA	1685														
615	UCUUCGUAAAGAACGGGUAU	35	615	UCUUCGUAAAGAACGGGUAU	35	633	AUUAAGGGAGCCGGUGGUCAU	1686														
633	UAAGGGAGCCGGUGGUCAU	36	633	UAAGGGAGCCGGUGGUCAU	36	651	AUGACCCACGGCUCCUA	1687														

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651	UAGCUAUGGCAUCGAUCUA	37	651	UAGCUAUGGCAUCGAUCUA	37	669	UAGAUICGAUGGCCAUAGCUA	1688
669	AAAGUCUUAAUGACUUAGGU	38	669	AAAGUCUUAAUGACUUAGGU	38	687	ACCUAAGUCAUAAAGCUUJ	1689
687	UGACGAGCUUAGGAUCUGAU	39	687	UGACGAGCUUAGGAUCUGAU	39	705	AUCAGUICGCCAAGCUCGUCA	1690
705	UCCCAUUAAGGAUUAUGAA	40	705	UCCCAUUAAGGAUUAUGAA	40	723	UUCAUAAAUCUUCAUAGGGAA	1691
723	ACAAAACUGGAACACUAAG	41	723	ACAAAACUGGAACACUAAG	41	741	CUAUGGUUCUCCAGUUUUUGU	1692
741	GCAUGGCAGUUGGCAUCUC	42	741	GCAUGGCAGUUGGCAUCUC	42	759	GAGUGGCCACUCGCCAUGC	1693
759	CCGUGAACUCACUGUGAG	43	759	CCGUGAACUCACUGUGAG	43	777	CUCACGAGGAGUUCACUGG	1694
777	GCUCAAUGGAGGUGCAUC	44	777	GCUCAAUGGAGGUGCAUC	44	795	GACUGGCCUCCAUUGAGC	1695
795	CAUCUGCUAUGGUUGCAAC	45	795	CAUCUGCUAUGGUUGCAAC	45	813	GUUGUGGACAUAGCGAGUG	1696
813	CAAUUUCUGGGCCCAGAU	46	813	CAAUUUCUGGGCCCAGAU	46	831	AUCUGGGCCACAGAAAUG	1697
831	UGGUUACCUCUJUGAUUGC	47	831	UGGUUACCUCUJUGAUUGC	47	849	GCAAUCAAGAGGGUACCCA	1698
849	CAUCAAAGAUUUUCUGCA	48	849	CAUCAAAGAUUUUCUGCA	48	867	UGCGAGAAAALCJUJUGAU	1699
867	ACGGCGGGCAAGUGCAUG	49	867	ACGGCGGGCAAGUGCAUG	49	885	CAUUGACUTUGCCCGGCCU	1700
885	GUGCACUCUUIUCGGAACAA	50	885	GUGCACUCUUIUCGGAACAA	50	903	UUGUUCGGAAAAGUGGCCAC	1701
903	ACUJGAAUACAUCGAGUCG	51	903	ACUJGAAUACAUCGAGUCG	51	921	CGACUCGAGGACCUUCUUC	1702
921	GAAGAGAGGUGGUUCUACUGC	52	921	GAAGAGAGGUGGUUCUACUGC	52	939	GCAGUAGACCCUCUUC	1703
939	CUGCCGUGACCAUGGCAU	53	939	CUGCCGUGACCAUGGCAU	53	957	AUGCUAUGGUUCACGGCA	1704
957	UGAAAUUUGGCCUGGUUCACU	54	957	UGAAAUUUGGCCUGGUUCACU	54	975	AGUGAACCGGCCAAUJUCA	1705
975	UGAGGCGCUCUGAUAAAGAGC	55	975	UGAGGCGCUCUGAUAAAGAGC	55	993	GCUCUUAUCAGAGGCCUCA	1706
993	CUACGAGCACCGACACCC	56	993	CUACGAGCACCGACACCC	56	1011	GGGUGUCUGGGUCGUJAG	1707
1011	CUUCGGAAAAUAAAGGUCC	57	1011	CUUCGGAAAAUAAAGGUCC	57	1029	GGCACUCUJUJUJUGGAAG	1708
1029	CAAGAAAUUUJUGACUUUC	58	1029	CAAGAAAUUUJUGACUUUC	58	1047	GAAUGUGUCAAAUJUUCUJUG	1709
1047	CAAAGGGGAAUGCCCAAAG	59	1047	CAAAGGGGAAUGCCCAAAG	59	1065	CUUGGGCAUJCCCCUUG	1710
1065	GUJGUUUCUJUJUAC	60	1065	GUJGUUUCUJUJUAC	60	1083	GUUAAGAGGAAACACAAAC	1711
1083	CUCAAAAGUCAAAGUCAU	61	1083	CUCAAAAGUCAAAGUCAU	61	1101	AAUGACUUUUGACUJUJUG	1712
1101	UCAACACCUGGUUGAAAAAG	62	1101	UCAACACCUGGUUGAAAAAG	62	1119	CUUUUCAACAGGUUGUJA	1713
1119	GAAAAAGACUGAGGGGUUC	63	1119	GAAAAAGACUGAGGGGUUC	63	1137	GAAACCCUCAGUCUUUUC	1714
1137	CAUGGGGGCUUAACGCCUCU	64	1137	CAUGGGGGCUUAACGCCUCU	64	1155	AGAGCGGUUAAGCCCCAUG	1715
1155	UGUGUACCCUGGUUGGUACU	65	1155	UGUGUACCCUGGUUGGUACU	65	1173	AGAUGCAACAGGGUJACACA	1716
1173	UCCACAGGGAGGUACAAU	66	1173	UCCACAGGGAGGUACAAU	66	1191	AUUGGUACACUCCUGUGGAA	1717
1191	UAUGGCACUJUGUACCUUIG	67	1191	UAUGGCACUJUGUACCUUIG	67	1209	CAAGGUAGACAAGUGGUJA	1718
1209	GAUGAAAUGUAUCAUCUGC	68	1209	GAUGAAAUGUAUCAUCUGC	68	1227	GCAAGAUUAUCUUUACU	1719
1227	CGAUGGAUJUUCAUUGCAG	69	1227	CGAUGGAUJUUCAUUGCAG	69	1245	CUGCCAGAAAGACUCAUCUG	1720
1245	GAUCUGGCACUUCUGAAA	70	1245	GAUCUGGCACUUCUGAAA	70	1263	UUUCAGAAAGUGGCACGU	1721
1263	AGCCACUJUGUACAUJUG	71	1263	AGCCACUJUGUACAUJUG	71	1281	ACAAUGUUCACAGUGGU	1722
1281	UGGCACUGAAAAUUJUGUU	72	1281	UGGCACUGAAAAUUJUGUU	72	1299	ACUJAAAUUUUCAGUGCCA	1723
1299	UAUUGAAGGACCUACUCA	73	1299	UAUUGAAGGACCUACUCA	73	1317	UGUAUGGUUCUJUCAUA	1724
1317	AUGUGGGGUACCUACUCAU	74	1317	AUGUGGGGUACCUACUCAU	74	1335	AGUAGGUAGGUACCCACAU	1725
1335	UAAUGCUCUJAGUGAAAUG	75	1335	UAAUGCUCUJAGUGAAAUG	75	1353	CAUUCUACUACAGCAUA	1726
1353	GCCCAUGUUCUGGCCUGUCA	76	1353	GCCCAUGUUCUGGCCUGUCA	76	1371	UUGACAGGGAGACAUUGGC	1727
1371	AGACCCAGAGAUJGGACCU	77	1371	AGACCCAGAGAUJGGACCU	77	1389	AGGUCCAAUCUCUGGUCAU	1728
1389	UGAGCAUAGGUUGGCAU	78	1389	UGAGCAUAGGUUGGCAU	78	1407	AUCUGCAACACUAUGCUA	1729

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1407	UUUUCACAACCACUCUAAAC	79	1407	UUUAUCAGAACCUCAAAAC	79	1425	GUUJUGAGGGGUUGUGUAAA	1730
1425	CAUUGAAACUCGACUCGCC	80	1425	CAUUGAAACUCGACUCGCC	80	1443	GCGGAGUCGAGGUUCAAUG	1731
1443	CAAGGGAGGUAGGACUAGA	81	1443	CAAGGGAGGUAGGACUAGA	81	1461	UCUAGUCGCCUACCCUUUG	1732
1461	AUGUUUUQGGGAGGCUUG	82	1461	AUGUUUUQGGGAGGCUUG	82	1479	CACACAGGCCUCCCCAAU	1733
1479	GUUUUGCCUAGUUGGCUUG	83	1479	GUUUUGCCUAGUUGGCUUG	83	1497	GCAGGCCAACAUAGGCAAAAC	1734
1497	CUUAAAUAAGCGGGCUAC	84	1497	CUUAAAUAAGCGGGCUAC	84	1515	GUAGGCACGCCUAAAUAAG	1735
1515	CUGGGUUCUCGUGCUAGU	85	1515	CUGGGUUCUCGUGCUAGU	85	1533	ACUAGACGAGGAACCCAG	1736
1533	UGCUGAUAAUGGCUAGGC	86	1533	UGCUGAUAAUGGCUAGGC	86	1551	GCCUGAGGCCAUAAUAGGA	1737
1551	CCAUACUGGCCAUACUGGU	87	1551	CCAUACUGGCCAUACUGGU	87	1569	ACCAGUAAAUGGCCAGUAGG	1738
1569	UGACAAUAGGGAGACCUUG	88	1569	UGACAAUAGGGAGACCUUG	88	1587	CAAGGUCCACAUUGUCA	1739
1587	GAAUGAGGAUCUCCUUGAG	89	1587	GAAUGAGGAUCUCCUUGAG	89	1605	CUCAAAGGAGAACCUAUUC	1740
1605	GAUACUGAGUGGAAACGU	90	1605	GAUACUGAGUGGAAACGU	90	1623	ACGUUCACGACUCAGUAUC	1741
1623	UGUUUACAUAAUACAUUUGU	91	1623	UGUUUACAUAAUACAUUUGU	91	1641	AACAAUUGGUAAAUGUAAAACA	1742
1641	UGGGCAUUIUICAUUUGAU	92	1641	UGGGCAUUIUICAUUUGAU	92	1659	AUUCAAAAAAUUCGCCA	1743
1659	UGAAAGAGGUUGGCCAUUU	93	1659	UGAAAGAGGUUGGCCAUUU	93	1677	AUUGAUGGCCACCUUUCA	1744
1677	UUUGGCAUUCUUCUGCU	94	1677	UUUGGCAUUCUUCUGCU	94	1695	AGCAGAGAAAAGAUIGCCAAA	1745
1695	UUCUACAAUGGCCUUAUU	95	1695	UUCUACAAUGGCCUUAUU	95	1713	AUUAAAAGGCACUUGUAGAA	1746
1713	UGACACAUAAAAGAGCUU	96	1713	UGACACAUAAAAGAGCUU	96	1731	AAGACUCUUUAUGGUUGUCA	1747
1731	UGAUUUACAAUGCUUUAAA	97	1731	UGAUUUACAAUGCUUUAAA	97	1749	UUUAAAAGACUUGUAAUCA	1748
1749	AACCAUUGGUUGGUUGGC	98	1749	AACCAUUGGUUGGUUGGC	98	1767	GCAGGACUCAACAAUUGGU	1749
1767	CGGUAAACAUAAAAGUACC	99	1767	CGGUAAACAUAAAAGUACC	99	1785	GGUAAUCUUAUAGUUAACCG	1750
1785	CAAGGGAAAGGCCGUAAAA	100	1785	CAAGGGAAAGGCCGUAAAA	100	1803	UUUACGGGUUUCCCUUUG	1751
1803	AGGGCUUUGAACAUUGGA	101	1803	AGGUUCUUGGAACAUUGGA	101	1821	UCCAAUUGGUUACGCCU	1752
1821	AACACAGAGAUCAGUUUU	102	1821	AACACAGAGAUCAGUUUU	102	1839	UAAAACACAGUGGUUGGU	1753
1839	AACACCCACUGUGGUUUU	103	1839	AACACCCACUGUGGUUUU	103	1857	AAAACACACAGUGGUUGGU	1754
1857	UCCCCUACAGGCCUGGCU	104	1857	UCCCCUACAGGCCUGGCU	104	1875	ACCAAGGCCUUGGGAGGGA	1755
1875	UGUUUAUCAGAUCAUUUU	105	1875	UGUUUAUCAGAUCAUUUU	105	1893	AAAAUUUAGUCUAAAACA	1756
1893	UGCGCGCACCUUGAUGCA	106	1893	UGCGCGCACCUUGAUGCA	106	1911	UGCAUCAAGGUUGGCCGCA	1757
1911	AGCAAAACCAUCUAAUCCU	107	1911	AGCAAAACCAUCUAAUCCU	107	1929	AGGAUUUAGUGGUUGGU	1758
1929	UGAUUUUCGAAAGGAGGCC	108	1929	UGAUUUUCGAAAGGAGGCC	108	1947	AGCUGUCUUCUUGCAAAUCA	1759
1947	UGUCACCAUACUUGGGU	109	1947	UGUCACCAUACUUGGGU	109	1965	ACCAUCACUUGGGUAGGCA	1760
1965	UAUUUCUGAACAGUCAA	110	1965	UAUUUCUGAACAGUCAA	110	1983	UAAUGACUUGUAGAAAUA	1761
1983	ACGUUCUUGGUUGGCCAUG	111	1983	ACGUUCUUGGUUGGCCAUG	111	2001	CAUGGGCUCUGACAGACGU	1762
2001	GGUUUUAUCUUCAGACUG	112	2001	GGUUUUAUCUUCAGACUG	112	2019	CAGGUUCUGAAAGUAAAACC	1763
2019	GCUCACCAACAGUGCUAU	113	2019	GCUCACCAACAGUGCUAU	113	2037	AAUGACACUUGGGUAGGCA	1764
2037	UAUUUAGGCCAUAGUAAUC	114	2037	UAUUUAGGCCAUAGUAAUC	114	2055	AGUJACAUUAUGCCAUAAA	1765
2055	UGGGGGCUUUGUACACAG	115	2055	UGGGGGCUUUGUACACAG	115	2073	CUGGUUCAGAACGACCCA	1766
2073	GACUUCUUCAGUGGUUGGU	116	2073	GACUUCUUCAGUGGUUGGU	116	2091	AGACAACCACUUGAGAAGUC	1767
2091	UAUUCUUCUUGGGCACUAC	117	2091	UAUUCUUCUUGGGCACUAC	117	2109	AGUAGUGGCCAAAAGAUUA	1768
2109	UGUUGAAAACAGUGGCCU	118	2109	UGUUGAAAACAGUGGCCU	118	2127	AGGGCCUGAGUUUUUCAACA	1769
2127	UAUCUUUAGGAUGGUAG	119	2127	UAUCUUUAGGAUGGUAG	119	2145	CUCAAUCCAUAAAAGAUUA	1770
2145	GCGAAACUUCAGUGCCAG	120	2145	GCGAAACUUCAGUGCCAG	120	2163	UCCUGCACUAGGUUCGCC	1771

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2163	AGUUGAAUUUCUCAAGGAU	121	2163	AGUUGAAUUCUCAAGGAU	121	2181	AUCGUUGAGAAUUCUACAU	1772
2181	UGCUCUUGGGAGAUUCUAAA	122	2181	UGCUCUUGGGAGAUUCUAAA	122	2199	UUUGAGAAUUCUCCCAAGCA	1773
2199	AUUUCUCAUJACGGGUU	123	2199	AUUUCUCAUJACGGGUU	123	2217	AACACCUGUAAUGAGAAA	1774
2217	UUUUGACAUJCGUCAAGGGU	124	2217	UUUUGACAUJCGUCAAGGGU	124	2235	ACCCUUGACGAGUUCAAA	1775
2235	UCAAAAUACAGGUGCUCA	125	2235	UCAAAAUACAGGUGCUCA	125	2253	UGAAGCAACCUGUAAUUGA	1776
2253	AGAUAAACAUCAAGGAUJGU	126	2253	AGAUAAACAUCAAGGAUJGU	126	2271	ACAAUCCUUGAUGUUAUCU	1777
2271	UGUAAAAGCUUCAUJGAU	127	2271	UGUAAAAGCUUCAUJGAU	127	2289	AUCAAUAGGCAUUUUAACA	1778
2289	UGUUGUUAACAAGGCACUC	128	2289	UGUUGUUAACAAGGCACUC	128	2307	GAGUGGUUGGUUAACAAACA	1779
2307	CGAAAUGUGCAUJGAUCAA	129	2307	CGAAAUGUGCAUJGAUCAA	129	2325	UUGAUCAUAGGCAUUUUCG	1780
2325	AGUCACUAUCGCCUGGCICA	130	2325	AGUCACUAUCGCCUGGCICA	130	2343	UGGCCAGCGGAUAGUGACU	1781
2343	AAAGUUGGGAUCAUCAAC	131	2343	AAAGUUGGGAUCAUCAAC	131	2361	GUUGAGUGAUCCGAAACUUU	1782
2361	CUUAGGGUGAAGUCAUC	132	2361	CUUAGGGUGAAGUCAUC	132	2379	GAUGAAGACUUCACCUAAG	1783
2379	CGCUCAAGCAAGGGACUU	133	2379	CGCUCAAGCAAGGGACUU	133	2397	AAGUUCGUUGGUUUGAGCG	1784
2397	UUACCGGUAGGUAGUUAACGU	134	2397	UUACCGGUAGGUAGUUAACGU	134	2415	ACGUUAACAGCAGGGUAA	1785
2415	UGGCAAGGAGCAGCUGCAA	135	2415	UGGCAAGGAGCAGCUGCAA	135	2433	UUGGAGCCUGGUUCUJGCCA	1786
2433	ACUACUCAUJCGCUUJAAAG	136	2433	ACUACUCAUJCGCUUJAAAG	136	2451	CUUJAAGGCGAUGAGUAGU	1787
2451	GGCACCAAAAGGAACUJACC	137	2451	GGCACCAAAAGGAACUJACC	137	2469	GGUUAUCUUCUUGUGUGC	1788
2469	CUIUCUJUGAAGGUAGUICA	138	2469	CUIUCUJUGAAGGUAGUICA	138	2487	UGAUAUCCCUUCAAGAAAG	1789
2487	ACAUGACACAGUACUJUACC	139	2487	ACAUGACACAGUACUJUACC	139	2505	GGUAGGUACUGGUCAUGU	1790
2505	CUCUGAGGGGGUJGUUCUC	140	2505	CUCUGAGGGGGUJGUUCUC	140	2523	GAGAAACCUCCUCAGAG	1791
2523	CAAGAACGGUGAAUCUGAA	141	2523	CAAGAACGGUGAAUCUGAA	141	2541	UUCGAGUUCACGUUCUJUG	1792
2541	AGCACUCUGAGCGCCGUU	142	2541	AGCACUCUGAGCGCCGUU	142	2559	AACGGGGGUUCUGAGUGGU	1793
2559	UGAUAGGUUCUCAAAUGGA	143	2559	UGAUAGGUUCUCAAAUGGA	143	2577	UCCAUUJUGUAGGUUAUCA	1794
2577	AGCUAUCCGUCCGACACCA	144	2577	AGCUAUCCGUCCGACACCA	144	2595	UGGUUGGGCGAAGGUAGGU	1795
2595	AGUCUGGUAAAUGGCCUC	145	2595	AGUCUGGUAAAUGGCCUC	145	2613	GAGGCGCAUUAACAGACU	1796
2613	CAUGCUCUJAGAGAUAAAG	146	2613	CAUGCUCUJAGAGAUAAAG	146	2631	CUUAUACUUCUAGAGGAAG	1797
2631	GGACAAAGAACAAUACUGC	147	2631	GGACAAAGAACAAUACUGC	147	2649	GCAGGUAUUCUUCUJUCC	1798
2649	CGCAUUGGUCCUGGUUUA	148	2649	CGCAUUGGUCCUGGUUUA	148	2667	UAAAACCAGGGAGAACAUUGC	1799
2667	ACUGGCUACAAACAUJGU	149	2667	ACUGGCUACAAACAUJGU	149	2685	GACAUJGUUUUUGGUCCAGU	1800
2685	CUUUCGCCUAAAAGGGGU	150	2685	CUUUCGCCUAAAAGGGGU	150	2703	ACCCCCUUUAAGGCAAAG	1801
2703	UGCACCAAUAAAAGGUUA	151	2703	UGCACCAAUAAAAGGUUA	151	2721	UACACCUUUAAAUGGUCA	1802
2721	AACCUUUUGGGAGAAUACU	152	2721	AACCUUUUGGGAGAAUACU	152	2739	AGUAUUCUUCUCAAGGU	1803
2739	UGUUGGGAGGUCAAGGU	153	2739	UGUUGGGAGGUCAAGGU	153	2757	ACCUUAGGUUCUCCAAACAA	1804
2757	UUAACAAAGGUAGGUAGGU	154	2757	UUAACAAAGGUAGGUAGGU	154	2775	GAUUCUACAUUCUUGUAA	1805
2775	CAACAUUUGGUJUGAUAAA	155	2775	CAACAUUUGGUJUGAUAAA	155	2793	UUCGAGUACAGGUAAAGGU	1806
2793	ACGUGGUAGACAAAGGUU	156	2793	ACGUGGUAGACAAAGGUU	156	2811	AAGCACUUJUGUCAACACGU	1807
2811	UAAUGAAAAGGUCCUGUC	157	2811	UAAUGAAAAGGUCCUGUC	157	2829	GACAGAGCACUUUCAUUA	1808
2829	CUACACUGGUAAAUCGGU	158	2829	CUACACUGGUAAAUCGGU	158	2847	ACCGGAUUCAACAGGUAG	1809
2847	UACCGAAGGUACUGGUU	159	2847	UACCGAAGGUACUGGUU	159	2865	AAACUUCAGUACUUCGGUA	1810
2865	UGCAUGGUUGGUAGGCAAG	160	2865	UGCAUGGUUGGUAGGCAAG	160	2883	CUCUGGUACAAACAGGUAG	1811
2883	GGCUUUGGUAGACUUA	161	2883	GGCUUUGGUAGACUUA	161	2901	UAAAUGUUCUCAACAGGCC	1812
2901	ACAAACCAGUUUCUGAUUC	162	2901	ACAAACCAGUUUCUGAUUC	162	2919	GAGAUCAAGAAAUCGGU	1813

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2919	CCUUACCAACAUU	163	2919	CCUUACCAACAUU	163	2937	AAUACCCAUU	1814
2937	UGAUCUUGAUGGAGU	164	2937	UGAUCUUGAUGGAGU	164	2955	ACUCCACUCAAGAUCA	1815
2955	UGUAGCUAACUACUUA	165	2955	UGUAGCUAACUACUUA	165	2973	UAGGAAGGUAGCUACU	1816
2973	AUUGAUGAUGCUUGGAA	166	2973	AUUGAUGAUGCUUGGAA	166	2991	UUCACCGAACAUAAA	1817
2991	AGAAAACUUUCAUCGU	167	2991	AGAAAACUUUCAUCGU	167	3009	ACGUAGAAGAUUUUUCU	1818
3009	UAUGUAUUGUUCUUCUAC	168	3009	UAUGUAUUGUUCUUCUAC	168	3027	GUAAAAGGAACAAUACUA	1819
3027	CCUCUCCAGAUGGAAAGAA	169	3027	CCUCUCCAGAUGGAAAGAA	169	3045	UUCUCCUACUUGGAGGG	1820
3045	AGAGGACGAUGGAGUGU	170	3045	AGAGGACGAUGGAGUGU	170	3063	ACACUCUGCAUGGUCCUCU	1821
3063	UGAGGAAGAGAAAUUGAU	171	3063	UGAGGAAGAGAAAUUGAU	171	3081	AUCAAUUCUUCUUCUCCUCA	1822
3081	UGAAAACCUGUAGAACUAG	172	3081	UGAAAACCUGUAGAACUAG	172	3099	CUCAUUUCUACAGGUUUUCA	1823
3099	GUACGGGUACAGGAGUAGU	173	3099	GUACGGGUACAGGAGUAGU	173	3117	AUCAUUUCUACGGGUAC	1824
3117	UUAUCAAGGUCCUCUCUG	174	3117	UUAUCAAGGUCCUCUCUG	174	3135	CAGGGGAGCCUUGUAAUA	1825
3135	GGAAAAUUGGUCCUCAGCU	175	3135	GGAAUUJUGGUCCUCAGCU	175	3153	AGCUGAGGCCAAAUC	1826
3153	UGAAAAACGUUCGAGUUGAG	176	3153	UGAAAAACGUUCGAGUUGAG	176	3171	CUCACUUCGAAACUJUUCUCA	1827
3171	GGAAAGAAAGAAGGAGAAC	177	3171	GGAAAGAAAGGAGAAC	177	3189	GUCUUCUUCUUCUUCUUC	1828
3189	CUGGCUGGGAUGUACUACU	178	3189	CUGGCUGGGAUGUACUACU	178	3207	AGUAGUAUCAUCAGGCCAG	1829
3207	UGAGCAAUCAGAUGUAG	179	3207	UGAGCAAUCAGAUGUAG	179	3225	CUCAAUCUCUAGAUUGCUCU	1830
3225	GCCAGAACAGAACCUACA	180	3225	GCCAGAACAGAACCUACA	180	3243	UGUAGGUUCUUGUCCGGC	1831
3243	ACCUUGAACAGAACGUAAU	181	3243	ACCUUGAACAGAACGUAAU	181	3261	UAAAUAUACCUUCUAGGU	1832
3261	UCAGUUUACUGGUUUUUA	182	3261	UCAGUUUACUGGUUUUUA	182	3279	UAAAUAUACCUAACUGA	1833
3278	AAAACUUAUCUGACAAUGUU	183	3279	AAAACUUAUCUGACAAUGUU	183	3297	AACAUUUCUGUAUJUJU	1834
3297	UGCCAUAAAUGGUUGAC	184	3297	UGCCAUAAAUGGUUGAC	184	3315	GUCAACACAUUAAUGGUUGCA	1835
3315	CAUCGUUAAGGGCACAA	185	3315	CAUCGUUAAGGGCACAA	185	3333	UUGUGCCUCCUJUACGAGU	1836
3333	AAGUGCUAAUCCUAUGGU	186	3333	AAGUGCUAAUCCUAUGGU	186	3351	CACCAUAGGAUUAUGCACUJ	1837
3351	GAUUGUAAAUGGUUGCUAAC	187	3351	GAUUGUAAAUGGUUGCUAAC	187	3369	GUUAGCAGCAUUAACAAUC	1838
3369	CAUACACCUGAAAACAUUGGU	188	3369	CAUACACCUGAAAACAUUGGU	188	3387	ACCAUUGUUACGGGUAGU	1839
3387	UGCGUGGUAGGUGGCA	189	3387	UGCGUGGUAGGUGGCA	189	3405	UGCACCCUGCUACACCA	1840
3405	ACUCAACAAAGGCAACAU	190	3405	ACUCAACAAAGGCAACAU	190	3423	AUUGGUUGCCUUGUUGAGU	1841
3423	UGGUGGCCAUGGAAAGGAG	191	3423	UGGUGGCCAUGGAAAGGAG	191	3441	CUCUUUUGCAUGGACCA	1842
3441	GAGUGAUGAUUACAUUAAG	192	3441	GAGUGAUGAUUACAUUAAG	192	3459	CUUAUUGUAUACAUACUC	1843
3459	GCUAAAUGGCCUCUACU	193	3459	GCUAAAUGGCCUCUACU	193	3477	UGUAGAGGGGCAUJUAGC	1844
3477	AGUAGGAGGGGUUGUUG	194	3477	AGUAGGAGGGGUUGUUG	194	3495	CAAAACAGACCCUCCUACU	1845
3495	GCUUUCUGGACAUAAUCU	195	3495	GCUUUCUGGACAUAAUCU	195	3513	AAGAUUAUGUCAGAAAGC	1846
3513	UGCUUAGAAGUGUCUGCAU	196	3513	UGCUUAGAAGUGUCUGCAU	196	3531	AUGGAGCACUUCUAGCA	1847
3531	UGUUGUUGGACCUAACUA	197	3531	UGUUGUUGGACCUAACUA	197	3549	UAGGUUAGGUUGCAACAA	1848
3549	AAUUGGAGGAGGACAU	198	3549	AAUUGGAGGAGGACAU	198	3567	GAUGGUCCUACUGCAUJU	1849
3567	CCAGCUUCUJUAGGGAGCA	199	3567	CCAGCUUCUAGGGAGCA	199	3585	UGCUUGCCUUAAGGAAGCUG	1850
3585	AUAUGAAAAUUUCAUUC	200	3585	AUAUGAAAAUUUCAUUC	200	3603	UGAAUJGAAAUUUCUAAU	1851
3603	ACAGGACACUUCUACUUGCA	201	3603	ACAGGACACUUCUACUUGCA	201	3621	UGCAAGGUAGGUACAUUGU	1852
3621	ACCAUUGGUUGGUAGGGC	202	3621	ACCAUUGGUUGGUAGGGC	202	3639	GCCUGUGGUAGGUACAUUGU	1853
3639	CAUAUUUGGUUGGUACCA	203	3639	CAUAUUUGGUUGGUACCA	203	3657	UGGUUUAGGCACAAUUAUG	1854
3657	ACUUCAGUCUUACAAUG	204	3657	ACUUCAGUCUUACAAUG	204	3675	CACUJGUAAAAGCUGAAGU	1855

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3675	GUGCGUGGAGACGGUUCGU	205	3675	GUGCGUGGAGACGGUUCGU	205	3693	ACGAACCCGUCUGGCAC	1856
3693	UACACAGGUUUUAUUGCA	206	3693	UACACAGGUUUUAUUGCA	206	3711	UGCAAUAUAAAACCUGUGUA	1857
3711	AGCUCAAUGCACAAAGCUCU	207	3711	AGCUCAAUGCACAAAGCUCU	207	3729	AAGAGCUUJUGCUAUAGACU	1858
3729	UUAUGAGCAGGUUGUCAUG	208	3729	UUAUGAGCAGGUUGUCAUG	208	3747	CAUGACAACCUGUCUAA	1859
3747	GAAGCCUUAUCUUGAUAAACUG	209	3747	GAAGCCUUAUCUUGAUAAACUG	209	3765	CAGGGUUAUCAAGAUAAUCC	1860
3765	UGUCGUAGAGGUAGGCA	210	3765	UGUCGUAGAGGUAGGCA	210	3783	UGCUUCCACUCUAGGCCUUC	1861
3783	ACCUAAAACAGAGGGAGGCCA	211	3783	ACCUAAAACAGAGGGAGGCCA	211	3801	UGGGCUUCUUGGUAGGU	1862
3801	ACCCAAAACACAGAAUUC	212	3801	ACCCAAAACACAGAAUUC	212	3819	GGAAUUCUUCUGGUUGGU	1863
3819	CAAAACUGAGGGAGAAUUC	213	3819	CAAAACUGAGGGAGAAUUC	213	3837	AGAUUUUCUCCUCAGUUUUG	1864
3837	UGUCGUACAGAAAGCCUGUC	214	3837	UGUCGUACAGAAAGCCUGUC	214	3855	GACAGGUUCUUGUACGACA	1865
3855	CGAUGUGAAGGCCAAAAAUU	215	3855	CGAUGUGAAGGCCAAAAAUU	215	3873	AUUUUUGGUUCUACAUCCG	1866
3873	UAAGGGCCUGCAUUGAUAG	216	3873	UAAGGGCCUGCAUUGAUAG	216	3891	CUCAUCAUAGCAGGCCUUA	1867
3891	GGUJUACCCAAACACUGAA	217	3891	GGUJUACCCAAACACUGAA	217	3909	UUCAGUGUUGGUUGGUAC	1868
3909	AGAAACUAAAGUUUCUUACC	218	3909	AGAAACUAAAGUUUCUUACC	218	3927	GGUAAAAGAACUUAUGUUU	1869
3927	CAAAUAGGUUACGUUUU	219	3927	CAAAUAGGUUACGUUUU	219	3945	AAACAGAGUAACUUAUUG	1870
3945	UGCUGAUACUACAUUGGUAG	220	3945	UGCUGAUACUACAUUGGUAG	220	3963	CUCUACAUUAGUAUACGCA	1871
3963	GCUUUJACCAUAGAUUCAG	221	3963	GCUUUJACCAUAGAUUCAG	221	3981	CUGAGAAUCAUGGUAAAGC	1872
3981	GAACAUGCULUAGGGUAA	222	3981	GAACAUGCULUAGGGUAA	222	3999	UUCACCUCUAAAGCAUGUIC	1873
3999	AGAU AUGCUUUCUUGUAG	223	3999	AGAU AUGCUUUCUUGUAG	223	4017	CUCAGAAAAGACAUACU	1874
4017	GAAGGAUGGACCUUACAU	224	4017	GAAGGAUGGACCUUACAU	224	4035	CAUGUAAGGGUACUCCUJC	1875
4035	GUAGGGUGAUGUUAUCACU	225	4035	GUAGGGUGAUGUUAUCACU	225	4053	AGUGAUAAACAUACCUAC	1876
4053	UAGUGGGUGAUACACUGU	226	4053	UAGUGGGUGAUACACUGU	226	4071	ACAAGUGAUACUACACUA	1877
4071	UGUUGGUAAUACCCUAAA	227	4071	UGUUGGUAAUACCCUAAA	227	4089	UUUGGGAGGUUAUACACAA	1878
4089	AAAGGCGUGGUGGACUACU	228	4089	AAAGGCGUGGUGGACUACU	228	4107	AGUGGGCAGCACGCCUJU	1879
4107	UGAGAUGCUCUCAAGACU	229	4107	UGAGAUGCUCUCAAGACU	229	4125	AGCUCUJUGAGACAUCLICA	1880
4125	UUUGAAGAAAGUGCCAGUU	230	4125	UUUGAAGAAAGUGCCAGUU	230	4143	AACUGGGCAGCUUUCUAAA	1881
4143	UGAUGAGUUAUAAACACG	231	4143	UGAUGAGUUAUAAACACG	231	4161	CGUGGUUAUACUCAUCA	1882
4161	GUACCCUGGAGCAAGGAGU	232	4161	GUACCCUGGAGCAAGGAGU	232	4179	ACAUCCUUGUCAGGGUAC	1883
4179	UGCUGGUUUACUACUUGAG	233	4179	UGCUGGUUUACUACUUGAG	233	4197	CUCAGUGUUAACCCAGCA	1884
4197	GGAAAGCUAAGACUGCUU	234	4197	GGAAAGCUAAGACUGCUU	234	4215	AAGAGCAGUCUAGCUICC	1885
4215	UAGAAAAGCAAAUCUGCA	235	4215	UAGAAAAGCAAAUCUGCA	235	4233	UGCGAGUUUUGCAUUCUJA	1886
4233	AUUUUAUGUACUACCUUCA	236	4233	AUUUUAUGUACUACCUUCA	236	4251	UGAAGGUUAUCAAAAUA	1887
4251	AGAAGGACCUAAUCGUAA	237	4251	AGAAGGACCUAAUCGUAA	237	4269	CUUCAGAUUAGGUUCUUC	1888
4269	GGAAAGAGAUUCUAGGAACU	238	4269	GGAAAGAGAUUCUAGGAACU	238	4287	AGUUCCUAGAACUCUUC	1889
4287	UGUAUCCUGGAAUJUGAGA	239	4287	UGUAUCCUGGAAUJUGAGA	239	4305	UCUCAAUUCAGGAAUACA	1890
4305	AGAAAUGCUUGCUACUGCU	240	4305	AGAAAUGCUUGCUACUGCU	240	4323	AGCAUGAGCAAGCAUUCU	1891
4323	UGAAGAGAGCAAGAAAUUA	241	4323	UGAAGAGAGCAAGAAAUUA	241	4341	UAUUUUUCUUGUCUUCU	1892
4341	AUGCCUUAUAGCAUGGAU	242	4341	AUGCCUUAUAGCAUGGAU	242	4359	AUCCAUGCAUAGGGCAUU	1893
4359	UGUUAUGAGCCAUAAUGGCA	243	4359	UGUUAUGAGCCAUAAUGGCA	243	4377	UGCCAUUAUGGGCUCUAC	1894
4377	AACCAUCCAACGUUAUUA	244	4377	AACCAUCCAACGUUAUUA	244	4395	AUACUDUACGUUGGAGGU	1895
4395	AAAAGGAAUAAAUCAA	245	4395	AAAAGGAAUAAAUCAA	245	4413	UUGGAAUAAAUCUUUA	1896
4413	AGAGGGCAUCCGUUGACAU	246	4413	AGAGGGCAUCCGUUGACAU	246	4431	AUAGCUAACGCAUCC	1897

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4431	UGGUGUCCGAUUCUUCUUU	247	4431	UGGUGUCCGAUUCUUCUUU	247	4449	AAAGAAGAAUCCGGACACCA	1898
4449	UUUAUACUAUAGAACCCU	248	4449	UUUAUACUAUAGAACCCU	248	4467	AGGCUCUUUACUAGGCCU	1899
4467	UGUAGCUUUCUAUUUAUCG	249	4467	UGUAGCUUUCUAUUUAUCG	249	4485	CGUAAAUAUAGAACCUACA	1900
4485	GAAGCUGAACUCUUCUAAU	250	4485	GAAGCUGAACUCUUCUAAU	250	4503	AUJUAGAGAGUACGUUCUJC	1901
4503	UGAGCCGGCUUGCUACAAUG	251	4503	UGAGCCGGCUUGCUACAAUG	251	4521	CAUJUGAGAACGGGCCUCA	1902
4521	GCCAAUUGGUUAUGUGACAA	252	4521	GCCAAUUGGUUAUGUGACAA	252	4539	UGUACAUAAACAAUUGGC	1903
4539	ACAUGGUUUUAUCCUUGAA	253	4539	ACAUGGUUUUAUCCUUGAA	253	4557	UUCAAAGAUAAAACCAUGU	1904
4557	AGAGGCUGCGCGUUAUG	254	4557	AGAGGCUGCGCGUUAUG	254	4575	CAUACAGCGCGAGCCUUCU	1905
4575	GCGUUCUCUUAAGCUCCU	255	4575	GCGUUCUCUUAAGCUCCU	255	4593	AGGAGCUUAGAGAACGCC	1906
4593	UGCCGUGAGUGUCAGUAICA	256	4593	UGCCGUGAGUGUCAGUAICA	256	4611	UGAUACUGACACUACGGCA	1907
4611	AUCACCGAUGCGUGUACU	257	4611	AUCACCGAUGCGUGUACU	257	4629	AGUAACAGCACUCCUGGUGAU	1908
4629	UACAUAAUAGGUAAUCUC	258	4629	UACAUAAUAGGUAAUCUC	258	4647	GAGGUACUCAUUAUGUA	1909
4647	CACUUCGCUCAUAAAGACA	259	4647	CACUUCGCUCAUAAAGACA	259	4665	UGUCUUGAGGACGUCCAGAU	1910
4665	AUCUGAGGAGGACUUAUGUA	260	4665	AUCUGAGGAGGACUUAUGUA	260	4683	UACAAAGUGGUCCUCAGAU	1911
4683	AGAAACAGUUCUUGUGCU	261	4683	AGAAACAGUUCUUGUGCU	261	4701	AGCCAAGAAAACGUUUUCU	1912
4701	UGGCUCUUAACAGAGAUUG	262	4701	UGGCUCUUAACAGAGAUUG	262	4719	CCAAUCUCUGUAAAGGCCA	1913
4719	GUCCUUAUUCAGGACAGCGU	263	4719	GUCCUUAUUCAGGACAGCGU	263	4737	ACGCUGGUCAAUAGGAC	1914
4737	UACAGAGUUAAGGUUGAA	264	4737	UACAGAGUUAAGGUUGAA	264	4755	UUCAAACCCUUAUCUGUA	1915
4755	AUUUCUUAAGCGGGUGAC	265	4755	AUUUCUUAAGCGGGUGAC	265	4773	GUACACCACGCCUUAAGAAA	1916
4773	CAAAAUUGGUACCAACACU	266	4773	CAAAAUUGGUACCAACACU	266	4791	AGUGGGGUACACAAUUUUG	1917
4791	UCUGGAGGGCCGUAGAG	267	4791	UCUGGAGGGCCGUAGAG	267	4809	CUCCACGGGUCCUCAGA	1918
4809	GUUUCAUICUUGCGGGUAG	268	4809	GUUUCAUICUUGCGGGUAG	268	4827	CUCCACGGGUAGGAAGAAC	1919
4827	GUUUCUUCUACUUGACAAA	269	4827	GUUUCUUCUACUUGACAAA	269	4845	UUJUGUAAGGUAGAAAGAAC	1920
4845	ACUAAAAGAGUCUCUUAUCC	270	4845	ACUAAAAGAGUCUCUUAUCC	270	4863	GGAUAAAGAGACUUUUAGU	1921
4863	CCUGGGGGAGGUAAAGACU	271	4863	CCUGGGGGAGGUAAAGACU	271	4881	AGCUUAACCUCCGCAGG	1922
4881	UAUAAAAGUGUUCACACU	272	4881	UAUAAAAGUGUUCACACU	272	4899	AGUGUGAAACCUUUUAUA	1923
4899	UGUGGACAACACAUUCUC	273	4899	UGUGGACAACACAUUCUC	273	4917	GAGGUUAGGUUGGUCCACCA	1924
4917	CCACACACAGCUUGGUAGU	274	4917	CCACACACAGCUUGGUAGU	274	4935	AUCCACAAAGGUUGGUUGG	1925
4935	UAUGUCUAGACAUUGGA	275	4935	UAUGUCUAGACAUUGGA	275	4953	UCCAUAGUCAUAGACAU	1926
4953	ACAGCAGUUCUGGUCCACA	276	4953	ACAGCAGUUCUGGUCCACA	276	4971	UGUIGGACCAACUGGUUGU	1927
4971	AUACUUGGAUGGUCCAGU	277	4971	AUACUUGGAUGGUCCAGU	277	4989	AUUGGACCAACUGGUAGU	1928
4989	UGUUAACAAAAAUAAACCU	278	4989	UGUUAACAAAAAUAAACCU	278	5007	AGGUUAAAUUUUGUAACA	1929
5007	UCAUGUAAAUCAGGGGU	279	5007	UCAUGUAAAUCAGGGGU	279	5025	ACCCUCAUGAUUUACAGUA	1930
5025	UAAGACUUUCUUGUACUA	280	5025	UAAGACUUUCUUGUACUA	280	5043	UAGUACAAAGAAACGUUA	1931
5043	ACCUUAGUGAUGACACACUA	281	5043	ACCUUAGUGAUGACACACUA	281	5061	UAGUGUGUCAUCACUAGGU	1932
5061	ACGUAGUGAAGCUUCUCAG	282	5061	ACGUAGUGAAGCUUCUCAG	282	5079	CUCGAAAAGCUUCACUACGU	1933
5079	GUACUACAUACUUCUAGU	283	5079	GUACUACAUACUUCUAGU	283	5097	AUCAGAGGUAGGUAGUAC	1934
5097	UGAGAGUUCUUGGUAGG	284	5097	UGAGAGUUCUUGGUAGG	284	5115	CCUACCAAGAAAACUCUCA	1935
5115	GUACAUAGUGUUCUUAAC	285	5115	GUACAUAGUGUUCUUAAC	285	5133	GUJJAAAAGCAAGACAUAC	1936
5133	CCACACAAAGAAAUGGAAA	286	5133	CCACACAAAGAAAUGGAAA	286	5151	UUUCCCCAUUUUUGGUUGG	1937
5151	AUUUCCUCAAGUUGGGGU	287	5151	AUUUCCUCAAGUUGGGGU	287	5169	ACCAACAAUCUUGGAAA	1938
5169	UUUACUUCUAAAUGG	288	5169	UUUACUUCUAAAUGG	288	5187	CCAUUUAAAUGGUAAA	1939

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5187	GCCUGAUAAACAUUGUUAU	289	5187	GGCUGAUAAACAUUGUUAU	289	5205	AUAACAAUUGUUUAUCAGCC	1940
5205	UUUGUCUAAAGGUUUUUAUA	280	5205	UUUGUCUAAAGGUUUUUAUA	290	5223	UAUAUAAAACACUAGACAAA	1941
5223	GCACCUUCAACGGCUUAGAA	291	5223	GCACCUUCAACGGCUUAGAA	291	5241	UUCAGCUGUUGUAAGUGCU	1942
5241	AGUAAAUAUCAAUGGCAAA	292	5241	AGUAAAUAUCAAUGGCAAA	292	5259	UGGUGCAUUAUUUGACU	1943
5259	AGCACUUCAGGAGGCUUUAU	293	5259	AGCACUUCAGGAGGCUUUAU	293	5277	AUAAGGCCUCUJUGAAGUGCU	1944
5277	UUAUAGAGCCCCGUGGUU	294	5277	UUAUAGAGCCCCGUGGUU	294	5295	ACCAGCACGGGCUUUAUA	1945
5295	UGAUGCGUACUUUGU	295	5295	UGAUGCGUACUUUGU	295	5313	ACAAAAGUUAGCAGCAUCA	1946
5313	UGCACUCUACUCCUAC	296	5313	UGCACUCUACUCCUAC	296	5331	GUAGCGAGUAGAGUGCA	1947
5331	CAGUAAAACAUUGUUGGC	297	5331	CAGUAAAACAUUGUUGGC	297	5349	GCCAAAGUUUAUACUG	1948
5349	CGAGCCUJGGUGAUGUAGA	298	5349	CGAGCCUJGGUGAUGUAGA	298	5367	UCUGACAUACACAAGCUUG	1949
5367	AGAAAACUAUGACCCAUU	299	5367	AGAAAACUAUGACCCAUU	299	5385	AAAGAUGGGGUCAUAGUUUICU	1950
5385	UCUACAGCAUGCUAAUUG	300	5385	UCUACAGCAUGCUAAUUG	300	5403	CAAAAUAGCAGCUGUAGA	1951
5403	GGAAUCUGCAAAGCGGAU	301	5403	GGAAUCUGCAAAGCGGAU	301	5421	AACUCGCUUJGGAGAUICC	1952
5421	UCUUAUAGUUGGUAAA	302	5421	UCUUAUAGUUGGUAAA	302	5439	UUUUAACACCCACAUUAAGA	1953
5439	ACAUUUGUGGUCAAGAAAACU	303	5439	ACAUUUGUGGUCAAGAAAACU	303	5457	AGUUUUJCUGACACAAAGU	1954
5457	UACUACCUUACGGGUUA	304	5457	UACUACCUUACGGGUUA	304	5475	UACACCCGUUAAGGUAGUA	1955
5475	AGAAGCGUGUAGUUAUG	305	5475	AGAAGCGUGUAGUUAUG	305	5493	CAUAUACAUACAGCUUCU	1956
5493	GGGUACUCUACUUAUGAU	306	5493	GGGUACUCUACUUAUGAU	306	5511	AUCUAAGAUAGAGUACCC	1957
5511	UAAUCUUAAGACAGGUU	307	5511	UAAUCUUAAGACAGGUU	307	5529	AACACCUUGCUUAAAGAUUA	1958
5529	UUCCAUUCCAUGUGUGU	308	5529	UUCCAUUCCAUGUGUGU	308	5547	ACACACAAUGGAAUGGAA	1959
5547	UGGUCGUGAUGGUACACAA	309	5547	UGGUCGUGAUGGUACACAA	309	5565	UUGGUUGUAGCAUCAGACCA	1960
5565	AUAUCCUAGAACAAAG	310	5565	AUAUCCUAGAACAAAG	310	5583	CUCUUGUAGUAGCAUAGAU	1961
5583	GUCCUCUJGUUUAUGAUG	311	5583	GUCCUCUJGUUUAUGAUG	311	5601	CAUCAUAAACAAAGAAC	1962
5601	GUCCUGCACCACCGUGUAG	312	5601	GUCCUGCACCACCGUGUAG	312	5619	CUCAGCAGGUUGUGCAGAC	1963
5619	GUAAAUAUACGCAAGGU	313	5619	GUAAAUAUACGCAAGGU	313	5637	ACCUUJGCUGUAUUUAUAC	1964
5637	UACAUUCUUAUGGGCAAU	314	5637	UACAUUCUUAUGGGCAAU	314	5655	AUUCGCACAUAAAGAUGUA	1965
5655	UGAGUACACUGGUAAACAU	315	5655	UGAGUACACUGGUAAACAU	315	5673	AUAGUUAACAGGUAGUACUCA	1966
5673	UCAGUGGGGUCAUACACU	316	5673	UCAGUGGGGUCAUACACU	316	5691	AGUGUUAUGACACACACUGA	1967
5691	UCAUUAUACUGGUAAAGGAG	317	5691	UCAUUAUACUGGUAAAGGAG	317	5709	CUCCUUJGCUGUAGUAAUGA	1968
5709	GCACCCUCAUCGUUAUJGAC	318	5709	GCACCCUCAUCGUUAUJGAC	318	5727	GUACAUACAGUAGGAGGU	1969
5727	GGAGCGUCACGUUAACAAAG	319	5727	GGAGCGUCACGUUAACAAAG	319	5745	CUUGUUAAGGUAGGUGCCG	1970
5745	GAUGUCAGGUACAAAGGA	320	5745	GAUGUCAGGUACAAAGGA	320	5763	UCCUUJGUACUACAGAC	1971
5763	ACCAAGGAAACAUUUC	321	5763	ACCAAGGAAACAUUUC	321	5781	GAAAACAUACAGUCACGGU	1972
5781	CUACAAGGAAACAUUUC	322	5781	CUACAAGGAAACAUUUC	322	5799	GUAGAUGGUUUCUUGUAG	1973
5799	CACUACAACCAUCAAGCCU	323	5799	CACUACAACCAUCAAGCCU	323	5817	AGCCUUGAUGGUAGUAGUG	1974
5817	UGUGUUGGUAAACUCGAU	324	5817	UGUGUUGGUAAACUCGAU	324	5835	AUCGAGGUUJUAGGACACA	1975
5835	UGGAGGUACUUAACAGAG	325	5835	UGGAGGUACUUAACAGAG	325	5853	CUCUGUGUAGGUACUCCA	1976
5853	GAUGGAACCAAAAUUUGAU	326	5853	GAUGGAACCAAAAUUUGAU	326	5871	AUCCCAUJJGUUCAUAC	1977
5871	UGGGUAAUAAAAGAU	327	5871	UGGGUAAUAAAAGAU	327	5889	AUCCUUJGUUAAAACCCA	1978
5889	UAAUGGUUACUUAACAGAG	328	5889	UAAUGGUUACUUAACAGAG	328	5907	CUCUGUUAAGGUAGGUAGU	1979
5907	GCAGCCUUAJAGCCUUGUA	329	5907	GCAGCCUUAJAGCCUUGUA	329	5925	UACAAAGGUUCUAGGGUGC	1980
5925	ACCAACCUAACCAUACCA	330	5925	ACCAACCUAACCAUACCA	330	5943	UGGUAAUGGUUGAGUUGGU	1981

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5943	AAAUGGGAGUUUUGAUAAU	331	5943	AAUUGGGAGUUUUGAUAAU	331	5661	AUUAUCAAAAUCUCGCAUUU	1982
5961	UUUCACAAACUCACAUGUUCU	332	5961	UUUCACAAACUCACAUGUUCU	332	5979	AGAACAUAGUGAGUUUUGAAA	1983
5979	UACACAAAAUUAUUGCUGAU	333	5979	UACACAAAAUUAUUGCUGAU	333	5997	AUCAGCAAAAUUUGUGUUA	1984
5997	UGAUUUUAAAUAUUGACAA	334	5997	UGAUUUUAAAUAUUGACAA	334	6015	UGCUAUUUGAUAAAUAU	1985
6015	AGGCUIUCACAAAGGCCGU	335	6015	AGGCUIUCACAAAGGCCGU	335	6033	AGCUGGUUCUUGUUGAAGCCU	1986
6033	UUCACGGAGAGCUAUCUGUC	336	6033	UUCACGGAGAGCUAUCUGUC	336	6051	GACAGAUAGCUCUCUGUGAA	1987
6051	CACAUUCUCCAGACUUG	337	6051	CACAUUCUCCAGACUUG	337	6069	CAAGCUGGGAGAAUUGUG	1988
6069	GAAUGGGGAUUGUAGGGCU	338	6069	GAAUGGGGAUUGUAGGGCU	338	6087	AGCACACUACAUGCCAUUC	1989
6087	UAUUGACUUAUAGACACUAU	339	6087	UAUUGACUUAUAGACACUAU	339	6105	AUAGUGUCUUAUAGCUAAUA	1990
6105	UUCAGGGAGGUUUAAGAAA	340	6105	UUCAGGGAGGUUUAAGAAA	340	6123	UUUCUUGAAAACUCGCGUAA	1991
6123	AGGUGCUAAAUUACUGCAU	341	6123	AGGUGCUAAAUUACUGCAU	341	6141	AUGGAGUAAAUAUGCACCU	1992
6141	UAAGCCAAUJGUUJGGCAC	342	6141	UAAGCCAAUJGUUJGGCAC	342	6159	GUGCCAAAACAUUGGCUUA	1993
6159	CAUUAACCAGGUUACAAAC	343	6159	CAUUAACCAGGUUACAAAC	343	6177	GGUUGUAGGCCUUGGUUAAUG	1994
6177	CAAGACAACGUUCAACCA	344	6177	CAAGACAACGUUCAACCA	344	6195	UGGUUUAACGUUGUCUUG	1995
6195	AAACACUUGGUUGUUACGU	345	6195	AAACACUUGGUUGUUACGU	345	6213	ACGUAAAACACCAAGGUUUU	1996
6213	UUGUCUJUGGAGUAAAG	346	6213	UUGUCUJUGGAGUAAAG	346	6231	CUUJGUACUCCAAAAGACAA	1997
6231	GCCAGGUAGAUACUCAAU	347	6231	GCCAGGUAGAUACUCAAU	347	6249	AUJUGAUAUACUACUGGC	1998
6249	UUCAUUJUGAAGUUCUGGCA	348	6249	UUCAUUJUGAAGUUCUGGCA	348	6267	UGCGAGAACUUAUAAUGAA	1999
6267	AGUAGAAAGACACAAAGGA	349	6267	AGUAGAAAGACACAAAGGA	349	6285	UCCUJUGUGUGUUCUUCAU	2000
6285	AUGGACAAUJCUCUGCUGU	350	6285	AUGGACAAUJCUCUGCUGU	350	6303	ACAAAGCAAGAUUGGUCCAUU	2001
6303	UGAAAAGUCAACACCCGAC	351	6303	UGAAAAGUCAACACCCGAC	351	6321	GGGGGUUGUUCUUCGUUUC	2002
6321	CUCUGAAAGGUAGUGGAA	352	6321	CUCUGAAAGGUAGUGGAA	352	6339	UUCUGACUACUUCUUGAG	2003
6339	AAAUCUACAUACAGAAAG	353	6339	AAAUCUACAUACAGAAAG	353	6357	CUCUCGUAGGUAGGAAUJU	2004
6357	GGAGGUCAUJAGUGUGAC	354	6357	GGAGGUCAUJAGUGUGAC	354	6375	GUACACUCUACGUACUCC	2005
6375	CGUGAAAACUACCGAAAGUU	355	6375	CGUGAAAACUACCGAAAGUU	355	6393	AACUUCGGGUAGUUUCACG	2006
6393	UGUAGGCCAAUJGUCAUUCU	356	6393	UGUAGGCCAAUJGUCAUUCU	356	6411	AAGUAGACAUJGUCCUA	2007
6411	UAAAACCAUCAGAUAGGGU	357	6411	UAAAACCAUCAGAUAGGGU	357	6429	ACCUUCAUCUGAUUGGUUA	2008
6429	UGUAAAAGUAAACACAGAG	358	6429	UGUAAAAGUAAACACAGAG	358	6447	CUCUJUGGUUACUUAACAA	2009
6447	GUAGGUCAUJAGGAUCUU	359	6447	GUAGGUCAUJAGGAUCUU	359	6465	AAGGAUCCUACUGGUCCUAAC	2010
6465	UAUGGCUGCUUAGGUUGGAA	360	6465	UAUGGCUGCUUAGGUUGGAA	360	6483	UCCACUAAAGCAGGCCAU	2011
6483	AAACACAAGCAUACAUUU	361	6483	AAACACAAGCAUACAUUU	361	6501	AUUGGUAAAGGUUGGUUUJU	2012
6501	UAGAAAACCUAAUAGACUU	362	6501	UAGAAAACCUAAUAGACUU	362	6519	AAGGUCAUJAGGUUUUUA	2013
6519	UUCACUAGCCUJAGGUUU	363	6519	UUCACUAGCCUJAGGUUU	363	6537	UAAAACCUAAGGUAGUGAA	2014
6537	AAAAACAAUJGCCACUCAU	364	6537	AAAAACAAUJGCCACUCAU	364	6555	AUGAGUGGCCAAUUGUUUU	2015
6555	UGGUAAUJGCCACUAAU	365	6555	UGGUAAUJGCCACUAAU	365	6573	AUJAUJUGCGAAUACCA	2016
6573	UAGUGUUCUJGGGUAAA	366	6573	UAGUGUUCUJGGGUAAA	366	6591	UJJACUCCAAAGGAACACUA	2017
6591	AUUUUGGCCUUAUGUCAA	367	6591	AUUUUGGCCUUAUGUCAA	367	6609	UUUGACAUAAAGCCAAAUU	2018
6609	ACCAUUCUAGGUAGGUCA	368	6609	ACCAUUCUAGGUAGGUCA	368	6627	UGCUJUGGUUAAGGUUGGU	2019
6627	AGCAAAUUACAAUCAAAU	369	6627	AGCAAAUUACAAUCAAAU	369	6645	AUJUGGUUGGUUAAGGUUGU	2020
6645	UUGCGCJAAGAGGUAGCA	370	6645	UUGCGCJAAGAGGUAGCA	370	6663	UGGUAAAACACACGUUGU	2021
6663	ACAAACGUGGUUUUAACAU	371	6663	ACAAACGUGGUUUUAACAU	371	6681	AUJUGGUAAAACACACGUUGU	2022
6681	UUUAUAGCCUUUAUGGUUU	372	6681	UUUAUAGCCUUUAUGGUUU	372	6699	AAACACAUAAAGGCCAUUA	2023

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6699	UACAUUAUUGUUCCAAUJUG	373	6699	UACAUUAUUGUUCCAAUJUG	373	6717	CAAUUJGGAAACAUAUAGUA	2024
6717	GUGUACUUUUACUAAAAGU	374	6717	GUGUACUUUUACUAAAAGU	374	6735	ACUUUUJGUAAAAGUACAC	2025
6735	UACCAAUUCUAGAAAUGA	375	6735	UACCAAUUCUAGAAAUGA	375	6753	UCUAAAUCUAGAAAUGGUA	2026
6753	AGCUUCAUCCUACAUACU	376	6753	AGCUUCAUCCUACAUACU	376	6771	AGUUGGUAGGUAGGUAGGU	2027
6771	UAUUGCJAAAUAUAGGUU	377	6771	UAUUGCJAAAUAUAGGUU	377	6789	AACAUUJGUAAAAGGAAU	2028
6789	UAAGAGUJGUUGGUAAAUA	378	6789	UAAGAGUJGUUGGUAAAUA	378	6807	UAUJUJUAGCAACACUCUUA	2029
6807	AUGUUUUGGAUGCCGGCAU	379	6807	AUGUUUUGGAUGCCGGCAU	379	6825	AAUGCCGGCAUCCAAACAU	2030
6825	UAUUUAUGGAAAGUACCC	380	6825	UAUUUAUGGAAAGUACCC	380	6843	GGGUAGACUUCACAUAAAUA	2031
6843	CAAAUUUCUAAAUGUUC	381	6843	CAAAUUUCUAAAUGUUC	381	6861	GAACAUUJGUAAAAGGUU	2032
6861	CACAAUCGCGUAGUGGCUA	382	6861	CACAAUCGCGUAGUGGCUA	382	6878	UAGGCCACAUAGCGAUUGUG	2033
6879	AUUGUUGUUAUGUAAUUGC	383	6879	AUUGUUGUUAUGUAAUUGC	383	6897	GCAAAUACIUUAACAAACAU	2034
6897	CUUAGGUUCUCUAAUCUGU	384	6897	CUUAGGUUCUCUAAUCUGU	384	6915	ACAGAUUJAGGAAACCUCUAG	2035
6915	UGUAACUGCGUUCGUUUGGU	385	6915	UGUAACUGCGUUCGUUUGGU	385	6933	ACCAAAAGCAGAGUACUAC	2036
6933	UGUACUCUUAUCUAAAUUJ	386	6933	UGUACUCUUAUCUAAAUUJ	386	6951	AAAAAUJGUAGGUAGGUAC	2037
6951	UGGUGGCUCCUUCUUAUGU	387	6951	UGGUGGCUCCUUCUUAUGU	387	6969	ACAAUAAAGAAGGAGGACCA	2038
6969	UAAUGGCGUUJAGGAAUUG	388	6969	UAAUGGCGUUJAGGAAUUG	388	6987	CAAUUCUCUAAAGGCCAUUA	2039
6987	GUACUUAUUCGCUAAC	389	6987	GUACUUAUUCGCUAAC	389	7005	GUUAGCAGAAUUAAGUAC	2040
7005	CGUACUACUAGGUJUC	390	7005	CGUACUACUAGGUJUC	390	7023	GAACUACUAGGUACUAC	2041
7023	CUGUGAAAGGUUCUUCUCCU	391	7023	CUGUGAAAGGUUCUUCUCCU	391	7041	AGGAAAAAGAACCUUCACAG	2042
7041	UGGCAGGCAUUAUGGUAGU	392	7041	UGGCAGGCAUUAUGGUAGU	392	7059	ACUUAACAAAUUGUGCUCCAA	2043
7059	UGGAUUAUGACUCCUUGAU	393	7059	UGGAUUAUGACUCCUUGAU	393	7077	AUCAGGGAGUCUAAUCCA	2044
7077	UCCUUAUACAGCUUAGUAA	394	7077	UCCUUAUACAGCUUAGUAA	394	7095	UICUAGGAGGUAGGUAGGU	2045
7095	AACCAUUCAGGUGGACAU	395	7095	AACCAUUCAGGUGGACAU	395	7113	AAUGGUACCCUGUAAUGGU	2046
7113	UCAUCAUGUACAAGGUAGAC	396	7113	UCAUCAUGUACAAGGUAGAC	396	7131	GUICUAGCUCUAGCAUGUAGA	2047
7131	CUUGACAAUUAUJAGGUUG	397	7131	CUUGACAAUUAUJAGGUUG	397	7149	CAGACCUAAAUAUJGUCAAG	2048
7149	GGCCGGCGUAGGGGUUJUG	398	7149	GGCCGGCGUAGGGGUUJUG	398	7167	CAAAACCCACUCAGGGGCC	2049
7167	GGCAUAUAUJGUUCACAA	399	7167	GGCAUAUAUJGUUCACAA	399	7185	UGUGAAACAACAUUAUGGCC	2050
7185	AAAAAUUCUUUUUAUUAUJA	400	7185	AAAAAUUCUUUUUAUUAUJA	400	7203	UAAAUAUAAAAGAAUJJU	2051
7203	AGGCUUUCAGCUUAAUG	401	7203	AGGCUUUCAGCUUAAUG	401	7221	CAUUAUCGUAAAAGACCU	2052
7221	GCAGGGGUUCUUCGGGUAU	402	7221	GCAGGGGUUCUUCGGGUAU	402	7239	AUAGCCAAAGAACCCUGC	2053
7239	UUUUGGUAGGUUCUUCGUAC	403	7239	UUUUGGUAGGUUCUUCGUAC	403	7257	GAUAGAAAAGACUAGGAA	2054
7257	CAGCAAUUCUUCGGCUAC	404	7257	CAGCAAUUCUUCGGCUAC	404	7275	CAUGAGGCCAAGAAUJUGCUG	2055
7275	GUUGGUUUAUCAUUAUGUAU	405	7275	GUUGGUUUAUCAUUAUGUAU	405	7293	AAUACUUAUAGUAAAACCAC	2056
7293	UGUACAAAUGGCACCCGUU	406	7293	UGUACAAAUGGCACCCGUU	406	7311	AACGGGGUGGCCAUUUGUAC	2057
7311	UUCUGGCAAUUGGUAGGAUG	407	7311	UUCUGGCAAUUGGUAGGAUG	407	7329	CAUCCUACCAUJUGCAGAA	2058
7329	GUACAUUCUUCUGCUUC	408	7329	GUACAUUCUUCUGCUUC	408	7347	AGAAGCAAAGAAGGUAC	2059
7347	UUUCUACUACAUUAUGGAAG	409	7347	UUUCUACUACAUUAUGGAAG	409	7365	CUIICCAUJUGGUAGGAAA	2060
7365	GAAGCUAUGGUUCAUACUAG	410	7365	GAAGCUAUGGUUCAUACUAG	410	7383	CAUGAUJAGGAAACAUAGCUC	2061
7383	GAAGGGGUUGGACCUUCUUG	411	7383	GAAGGGGUUGGACCUUCUUG	411	7401	CGAAGGGGUUGGACCAUC	2062
7401	GACUUGGUAGGUAGGUACAU	412	7401	GACUUGGUAGGUAGGUACAU	412	7419	AUAGCACAUAGGUAGGUAC	2063
7419	UAAGGGCAAUCUGGCCACAA	413	7419	UAAGGGCAAUCUGGCCACAA	413	7437	UGUUGGCACGGAUUGGCCUUA	2064
7437	ACGGCUUAGGUACAAACU	414	7437	ACGGCUUAGGUACAAACU	414	7455	AGUUGUACACCUAACCGCGU	2065

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7455	UAUUGUUAAUGGCAUGGAAG	415	7455	UAUUGUUAAUGGCAUGGAAG	415	7473	CUUCAUAGCCAUUAAACAAUA	2066
7473	GAGAUCUUCUUCUAGUCUAU	416	7473	GAGAUCUUCUUCUAGUCUAU	416	7491	AUAGACAUAGAAAAGAUUCUC	2067
7491	UGCAAAUAGGAGGGCGGGC	417	7491	UGCAAAUAGGAGGGCGGGC	417	7509	GCAACGGCCCUCCAUUUGCA	2068
7509	CUUCUGCAAGACUCAAAU	418	7509	CUUCUGCAAGACUCAAAU	418	7527	AUUGUGAGCUUJUGCAGAAG	2069
7527	UUGGAAUUGGUCCAUUJGU	419	7527	UUGGAAUUGGUCCAUUJGU	419	7545	ACAAUUGAGACAAUUCCAA	2070
7545	UGACACAUUUUUGGACUGGU	420	7545	UGACACAUUUUUGGACUGGU	420	7563	ACOAUGCAAAAUUGGUCA	2071
7563	UAGUACAUCAUUAUGUGAU	421	7563	UAGUACAUCAUUAUGUGAU	421	7581	AUCACUAAUGGAUGUACUA	2072
7581	UGAAGUUGGUCCUGGUUUUG	422	7581	UGAAGUUGGUCCUGGUUUUG	422	7599	CAAUCACGAGCACUUCUA	2073
7599	GUACUCOAGUAAAAGA	423	7599	GUACUCOAGUAAAAGA	423	7617	UCUUUUAACUJGGAGGAGAC	2074
7617	ACCAAUACUACCCUACUGAC	424	7617	ACCAAUACUACCCUACUGAC	424	7635	GUCAGUAGGGGUUAUGGU	2075
7635	CCAGGUCAUCGUAAUJGUU	425	7635	CCAGGUCAUCGUAAUJGUU	425	7653	AACAAUUAUCAGGUACUGG	2076
7653	UGAUAGUGGUUGGUUGGAAA	426	7653	UGAUAGUGGUUGGUUGGAAA	426	7671	UUUCACGACACUACUA	2077
7671	AAAUGGGCGGUUCUACCCUC	427	7671	AAAUGGGCGGUUCUACCCUC	427	7689	GAGGUUGAGGCCAUUJ	2078
7689	CUACUUUGACAAGGCUGGU	428	7689	CUACUUUGACAAGGCUGGU	428	7707	ACCAAGCCUJGUCAAAAGUAG	2079
7707	UCAAAAAGACCUCUAGAGAGA	429	7707	UCAAAAAGACCUCUAGAGAGA	429	7725	UCUCUCAUAGGUCCUUUGA	2080
7725	ACAUCCGGCUCCUCCAUUUJ	430	7725	ACAUCCGGCUCCUCCAUUUJ	430	7743	AAAUGGGAGAGGGGAUGU	2081
7743	UGUCAAAUUAUGACAAUUUG	431	7743	UGUCAAAUUAUGACAAUUUG	431	7761	CAAUUGGUCAAAUUGACA	2082
7761	GAGAGCUAACAAACAUAAA	432	7761	GAGAGCUAACAAACAUAAA	432	7779	UUUAGUGUJGUUGGUAGCUC	2083
7779	AGGUUCACUGCCAUUJAU	433	7779	AGGUUCACUGCCAUUJAU	433	7797	AUAAAUAUGGCGGUAGAACCU	2084
7797	UGUCAUAGUUUUUUGGUJGGC	434	7797	UGUCAUAGUUUUUUGGUJGGC	434	7815	GCAUCAAAAACUAUGACAA	2085
7815	CAAGGUCAAAUGGCAGGAG	435	7815	CAAGGUCAAAUGGCAGGAG	435	7833	CUCGUCCAUJGUUGACUUG	2086
7833	GUCGUCCUUAAGUICUGCU	436	7833	GUCGUCCUUAAGUICUGCU	436	7851	AGGAGCUUAGAAGGAGAGAC	2087
7851	UUCUGUGGUACUACAGUCAG	437	7851	UUCUGUGGUACUACAGUCAG	437	7869	CUGACGUAGUJGUACACAGAA	2088
7869	GCUGAUGUGCCAACCUJAU	438	7869	GCUGAUGUGCCAACCUJAU	438	7887	AUAGGUUGGCACAUACAGC	2089
7887	UCUGUUGGUUGGUACCAAGCU	439	7887	UCUGUUGGUUGGUACCAAGCU	439	7905	AGCUUUGGUAGACACAGA	2090
7905	UCUJGUUAUCAGACGUUGGA	440	7905	UCUJGUUAUCAGACGUUGGA	440	7923	UCCAACGUUGGUACAUACAGA	2091
7923	AGAUAGUACUGGUUUCC	441	7923	AGAUAGUACUGGUUUCC	441	7941	GGAAACUUCAGUACUAUCU	2092
7941	CGUJAAAGAUGUUUAGUCC	442	7941	CGUJAAAGAUGUUUAGUCC	442	7959	AGCAUCAAAUCAUUACUACG	2093
7959	UUAUGUGGUACCCUUUICA	443	7959	UUAUGUGGUACCCUUUICA	443	7977	UGAAAAGGUUGGUACAUAA	2094
7977	AGCAACUUUUJAGGUUCCU	444	7977	AGCAACUUUUJAGGUUCCU	444	7995	AGGAACACUAAAAGGUUCU	2095
7995	UAUUGAAAACCUAAGGCA	445	7995	UAUUGAAAACCUAAGGCA	445	8013	UGCUUUAAGUUUUCUCAUA	2096
8013	ACUUGUUGGUACAGGUAC	446	8013	ACUUGUUGGUACAGGUAC	446	8031	GUGAGCUGUAGCAACAGU	2097
8031	CAGCGAGGUAGCAAGGGU	447	8031	CAGCGAGGUAGCAAGGGU	447	8049	ACCUUUGCUACUCGCUUG	2098
8049	UGUAGGUUUJAGGUUGGU	448	8049	UGUAGGUUUJAGGUUGGU	448	8067	GACACCAUCUAAAGGUACUA	2099
8067	CCUJGUACAUUCGGGUCA	449	8067	CCUJGUACAUUCGGGUCA	449	8085	UGACACGAAUGGUAAAAGG	2100
8085	AGCUGGCCGACAAGGGGU	450	8085	AGCUGGCCGACAAGGGGU	450	8103	AACACCUJGUUGGGCAGCU	2101
8103	UGUJGUACCGGUUGGUAC	451	8103	UGUJGUACCGGUUGGUAC	451	8121	GUCAACAUUGGUACUAACA	2102
8121	CACAAAGGAUGGUUJGUAA	452	8121	CACAAAGGAUGGUUJGUAA	452	8139	UUCAAUAAUCUCCUUUGUG	2103
8139	AUGUCUCAACUUUCAU	453	8139	AUGUCUCAACUUUCAU	453	8157	AUUGAAAAGGUUGAGACAU	2104
8157	UCACUCUGACUUJGUAGUG	454	8157	UCACUCUGACUUJGUAGUG	454	8175	CACUJGUACGUAGAGUGA	2105
8175	GACAGGUGGAGAGGUUAC	455	8175	GACAGGUGGAGAGGUUAC	455	8193	GUUACAACUGGUACCUUC	2106
8193	CAAUUUCAUGGUCCUCCAU	456	8193	CAAUUUCAUGGUCCUCCAU	456	8211	AUAGGUGGAGGUAAAUG	2107

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8211	UUUAAGGUUAGAAACAUUG	457	8211	UUUAAGGUUAGAAACAUUG	457	8228	CAUGUUUUCAACCUCUAAA	2108
8229	GACGCCCGAGAACUUCGGC	458	8229	GACGCCCGAGAACUUCGGC	458	8247	GCCAAAGAUCUCUGGGCGUC	2109
8247	CGCAUGUUAUUGACGUAAA	459	8247	CGCAUGUUAUUGACGUAAA	459	8265	AUUACAGGUAAAUCAUUGC	2110
8265	UGCAAGGCAUUAUAGUCC	460	8265	UGCAAGGCAUUAUAGUCC	460	8283	GGCAUUGAUAGGCCUUGGA	2111
8283	CCAAGUAGCAAAAGUCAC	461	8283	CCAAGUAGCAAAAGUCAC	461	8301	GUGGUUUCGUACUUGGG	2112
8301	CAAUGUUIUACUACUUGG	462	8301	CAAUGUUIUACUACUUGG	462	8319	CCAGAUAGGAGAAACAUUG	2113
8319	GAAUGUAAAAGACUACAU	463	8319	GAAUGUAAAAGACUACAU	463	8337	CAUGUAGGUUUCUACAUUC	2114
8337	GUCCUUAUCUGAACGCUG	464	8337	GUCCUUAUCUGAACGCUG	464	8355	CAGCUGGUUCAGGUAAAGAC	2115
8355	GCGUAAACAAUUCGUAGU	465	8335	GCGUAAACAAUUCGUAGU	465	8373	ACUAGAAUUGUUUACG	2116
8373	UGCUUGCCAAGAACAAAC	466	8373	UGCUUGCCAAGAACAAAC	466	8391	GUUGGUUCUUGGCAGCA	2117
8391	CAUACCUUUCUAGCUAACU	467	8391	CAUACCUUUCUAGCUAACU	467	8409	AGUUAUCUAAAAGGUUAUG	2118
8409	UGUGGUCAUACUAGACAG	468	8409	UGUGGUCAUACUAGACAG	468	8427	CGUJCUAGGUUAGGCCACAA	2119
8427	GGUUGGUCAUAGCUAACU	469	8427	GGUUGGUCAUAGCUAACU	469	8445	AGUUAUGACAUAGACAACC	2120
8445	UACUAAAACUCACUCAAG	470	8445	UACUAAAACUCACUCAAG	470	8463	CGUJAGGUAGGUUUUAGUA	2121
8463	GGGGGGUAAGAUUGUAGU	471	8463	GGGGGGUAAGAUUGUAGU	471	8481	ACUACAAUCUUAACCCACCC	2122
8481	UACUUGUUUAAAUCUUAUG	472	8481	UACUUGUUUAAAUCUUAUG	472	8499	CAUAGUUUAAAACAAGUA	2123
8499	GCUUAAGGCCACAUUUG	473	8499	GCUUAAGGCCACAUUUG	473	8517	CAAUAAUGGGCUUAAAGC	2124
8517	GGGGGUUUCUUGGUCAUUG	474	8517	GGGGGUUUCUUGGUCAUUG	474	8535	CAAUIGCAGCAAGAACGGCAC	2125
8535	GGUUGGUUAUUAUCGUUAUG	475	8535	GGUUGGUUAUUAUCGUUAUG	475	8553	CAUAAACGUAUUAACAAAC	2126
8553	GCCAGGUACAAUACAUUGCA	476	8553	GCCAGGUACAAUACAUUGCA	476	8571	UGACAAUGGUAGUACUGGGC	2127
8571	AUCCAUGGAUUCUACACA	477	8571	AUCCAUGGAUUCUACACA	477	8589	UGUGUAAACGUAGUUGGAUJ	2128
8589	AAUAGAAAUCAUUGGUAC	478	8589	AAUAGAAAUCAUUGGUAC	478	8607	GUAGUAAACGUAGUUGGU	2129
8607	CAAAGCCAUUCAGGAGGU	479	8607	CAAAGCCAUUCAGGAGGU	479	8625	ACCAUCCGUAGGUUUUUG	2130
8625	UGUCACUCUGGACAUCAU	480	8625	UGUCACUCUGGACAUCAU	480	8643	AAUGAUGGUACAGAGUGACA	2131
8643	UUCUACUGAUGAUUGUUU	481	8643	UUCUACUGAUGAUUGUUU	481	8661	AAAAACAAUCAUCAGUGAA	2132
8661	UGCCAAAUAACAUAGCUGG	482	8661	UGCCAAAUAACAUAGCUGG	482	8679	ACCGAGCAUUGUUUUGCA	2133
8679	UUUUGACGCCAGGUUAGC	483	8679	UUUUGACGCCAGGUUAGC	483	8697	GCUAAAACCAUAGGUAAA	2134
8697	CCAGCGGUUGGUUGGUCAUAC	484	8697	CCAGCGGUUGGUUGGUCAUAC	484	8715	GUAGUAAACCAACCGCUGG	2135
8715	CAAAAAGUAGCAAAAGCUG	485	8715	CAAAAAGUAGCAAAAGCUG	485	8733	GCAGCUUUUGUCAUAAAUG	2136
8733	CCCGUAGGUAGGUACUAC	486	8733	CCCGUAGGUAGGUACUAC	486	8751	GAUAGCAGCUACUACAGGG	2137
8751	CAUUAAGGUAGGUAGGU	487	8751	CAUUAAGGUAGGUAGGU	487	8769	ACCAUACUUCGUAGUUAUG	2138
8769	UUUCAUAGGUAGGUACUUA	488	8769	UUUCAUAGGUAGGUACUUA	488	8787	UAAGGCCAGGCACUAGAAA	2139
8787	ACCGGGGUACUGGUUGGAGA	489	8787	ACCGGGGUACUGGUUGGAGA	489	8805	UCUCAAGCACGUACCCGGU	2140
8805	AGCAAUCAUAGGUAGCUUC	490	8805	AGCAAUCAUAGGUAGCUUC	490	8823	GAAGUACCAUUGAUUGCU	2141
8823	CUUGCAUUCUACCUUCGU	491	8823	CUUGCAUUCUACCUUCGU	491	8841	ACGAGGUAGAAAUGCAAG	2142
8841	UGUUUUUAGUGGUUGGG	492	8841	UGUUUUUAGUGGUUGGG	492	8859	GCCAAACGCAUAAAACA	2143
8859	CAACAUUUGGUACACCU	493	8859	CAACAUUUGGUACACCU	493	8877	AGGUUGGUAGGCAAAUGUUG	2144
8877	UCCAAACCUUAGGUAU	494	8877	UCCAAACCUUAGGUAU	494	8895	AUACUCAUAGGUUGGGAA	2145
8895	UAGUGAUUUUCGUACCU	495	8895	UAGUGAUUUUCGUACCU	495	8913	AGGGGUAGGCAAAUACUA	2146
8913	UGCUUUGGUUGGUUGGG	496	8913	UGCUUUGGUUGGUUGGG	496	8931	ACGAGCAAGAACGGCAAGCA	2147
8931	UGAGUGUACAAUUIUUAAG	497	8931	UGAGUGUACAAUUIUUAAG	497	8949	CUJAAAUAUUGUACACUCA	2148
8949	GGAGGUUAUGGGCAAAACC	498	8949	GGAGGUUAUGGGCAAAACC	498	8967	AGGUUUGCCCCAUAGCAUCC	2149

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8967	UGGCCAUUUGGUAGAC	499	8967	UGGCCAUUUGGUAGAC	499	8985	GUCAUAAACAUAUAGGGCACA	2150
8985	CACUAAUUGGUAGGGU	500	8985	CACUAAUUGGUAGGGU	500	9003	ACCCUCUAGGCAAAUJAGUG	2151
9003	UUCUAAUUCUAAUAGUGAG	501	9003	UUCUAAUUCUAAUAGUGAG	501	9021	CUCAUAAAGGAAUAGAA	2152
9021	GCUUCGUCCAGACUCGU	502	9021	GCUUCGUCCAGACUCGU	502	9039	ACGAGUGUGGGACAGGC	2153
9039	UU AUG GGU U A U G G G U	503	9039	UU AUG GGU U A U G G U	503	9057	ACCAUCCAUAGCACAUAA	2154
9057	U U C C A U C A U A C U U I C C U	504	9057	U U C C A U C A U A C U U I C C U	504	9075	AGGA AAC U G G U A U G A U G G A A	2155
9075	U A A C A C U U A C C U G G G G U	505	9075	U A A C A C U U A C C U G G G G U	505	9093	ACCU CAG G J U A U G G U U A	2156
9093	U U C G U U A G G A U G A A C A	506	9093	U U C G U U A G G A U G A A C A	506	9111	U G G U A C U A C U A C U A C G A A A	2157
9111	A A C U U U J G U A G G C U A G U A C	507	9111	A A C U U U J G U A G G C U A G U A C	507	9129	GUACU CAG G A C I C A A A A G U U	2158
9129	C U G U A G C A U G G U A C A U G C	508	9129	C U G U A G C A U G G U A C A U G C	508	9147	G C A U G U A C C A U G U C U A C A G	2159
9147	C G A A A G G U C A G A A G U A G G U	509	9147	C G A A A G G U C A G A A G U A G G U	509	9165	ACCU A U C U C U G G C U U U C U G	2160
9165	U A U U U G C C U A U C U A C C A G U	510	9165	U A U U J G C C U A U C U A C C A G U	510	9183	ACU G G U A G J U A G G C A A A U A	2161
9183	U G G U A G G G G U U C U U A A U	511	9183	U G G U A G G G G U U C U U A A U	511	9201	A U U A G A A C C A U C U A C C A	2162
9201	U A A U G G C A U U A C A G A G C U	512	9201	U A A U G G C A U U A C A G A G C U	512	9219	A G C U C U G U A A J G C U C U A U U A	2163
9219	U C U A U C A G G A G U U I C U G U	513	9219	U C U A U C A G G A G U U I C U G U	513	9237	A C A G A A A C U C U C G U A U G A A	2164
9237	U G G U G U U G A U G G C G A U G A A U	514	9237	U G G U G U U G A U G G C G A U G A A U	514	9255	A U U C A U G C A U C A A C A C C A	2165
9255	U C U C A U A G C U A A C A U C U U U	515	9255	U C U C A U A G C U A A C A U C U U U	515	9273	A A A G A U G G U U A G C U A U G A G A	2166
9273	U A C U C C U C U U G G C A A C C U	516	9273	U A C U C C U C U U G G C A A C C U	516	9291	A G G U U G C A C A A G A G G A G U	2167
9291	U G G U G G G U G C U U J A U G U G	517	9291	U G G U G G G U G C U U J A U G U G	517	9309	C A C A U C U A A A G C A C C C A C A	2168
9309	G U C U G C U C U A G U A G G G C U	518	9309	G U C U G C U C U A G U A G G G C U	518	9327	A G C C A U C A U U A G G C A G A C	2169
9327	U G G U G G U A U U A U G G C C A U A	519	9327	U G G U G G U A U U A U G G C C A U A	519	9345	U A U G G C A U A U A U A C C A C C A	2170
9345	A U J G G G A C U U G G C U G C C	520	9345	A U J G G G A C U U G G C U G C C	520	9363	G G G A G C A C A A G C U C A C C A U	2171
9363	C U J A C U C U U A G G A A U U C	521	9363	C U A C U C U U A G G A A U U C	521	9381	G A A U U C U A U A A G U A G U A G	2172
9381	C A G A C G G U G U U U U G G I G A G	522	9381	C A G A C G G U G U U U U G G I G A G	522	9399	C U C A C C A A A C C A G U C U G C	2173
9399	G U C A C A C C A U G G U G U G C U	523	9399	G U C A C A C C A U G G U G U G C U	523	9417	A G C A A C A A C A U G G U G U A C	2174
9417	U G C U A A U G G A C U U U G G U U U	524	9417	U G C U A A U G G A C U U U G G U U U	524	9435	A A A C C A A A G G C A U U A G G A	2175
9435	U U U G A U G G U C U U C A C U A A	525	9435	U U U G A U G G U C U U C A C U A A	525	9453	U A U A G G U A A A G G A C A U C A A A	2176
9453	A C U C U G C U C U G G A C C A G C U	526	9453	A C U C U G C U C U G G A C C A G C U	526	9471	A G C U G G U A C C A G A C A G G U	2177
9471	U U A C A G G C U U C U G C C G G G A	527	9471	U U A C A G G C U U C U G C C G G G A	527	9489	U C C G G C A G A A A G G C U G U A A	2178
9489	A G U C U A C U C A G U C U U U A C	528	9489	A G U C U A C U C A G U C U U U A C	528	9507	G U A A A A G A C U G A G U A G A C U	2179
9507	C U U G A C U G A C A U C U A U	529	9507	C U U G A C U G A C A U C U A U	529	9525	A U G G A A U G G C A A U G G A	2180
9525	U U U C A C C A U G A G U U U C A	530	9525	U U U C A C C A U G A G U U U C A	530	9543	U G A A A A C U A U G G U G A A A A	2181
9543	A U U C U U G G C U C A C C U C A A	531	9543	A U U C U U G G C U C A C C U C A A	531	9561	U U G A A G G G U G A G C C A A G A A U	2182
9561	A U G G U U U G C C A U G U U U C U	532	9561	A U G G U U U G C C A U G U U U C U	532	9579	A G A A A A C A U G G C A A A C C A U	2183
9579	U C C U A U J G U G C C U U U U G G	533	9579	U C C U A U J G U G C C U U U U G G	533	9597	C C A A A A A G G C A C A A U G G A	2184
9597	G A U A A C A G G C A A C U A G U A	534	9597	G A U A A C A G G C A A C U A G U A	534	9615	U A C A U A G G U A U G G C U U A C	2185
9615	A U U C U U G G C U U U C U C U G A A G	535	9615	A U U C U U G G C U U U C U C U G A A G	535	9633	C U U C A G A A A U A C A G A A U	2186
9633	G C A C U G C C A U U G G U C U U U	536	9633	G C A C U G C C A U U G G U C U U U	536	9651	A A A G C A C C A A U G G C A G G U C	2187
9651	U A A C A C U A C U U A G G A A A	537	9651	U A A C A C U A C U U A G G A A A	537	9669	U U J U C C U A A G A U G G U U U A	2188
9669	A A G A G U C A U G U U U A U G G A	538	9669	A A G A G U C A U G U U U A U G G A	538	9687	U C C A U U J A A C A G U C U U	2189
9687	A G U U A C A U U U A G U A C C U U C	539	9687	A G U U A C A U U U A G U A C C U U C	539	9705	G A I G G U A C U A A U G U A A C U	2190
9705	C G A G G A G G C U G C U U U G G U	540	9705	C G A G G A G G C U G C U U U G G U	540	9723	A C A C A A G G C A G C C U C U G	2191

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9723	UACCUUUUJGCUCAACAAG	541	9723	UACCUUUUJGCUCAACAAG	541	9741	CJUUGAGGAAAGGUUA	2192
9741	GGAAAUGGUACCUAAAUG	542	9741	GGAAAUGGUACCUAAAUG	542	9759	CAAUUUJGGGUACUUUCC	2193
9759	GCGUAGCGAGACACGUUG	543	9759	GCGUAGCGAGACACGUUG	543	9777	CAACAGGUCUCGUACGC	2194
9777	GCCACUJACACAGUAAAC	544	9777	GCCACUJACACAGUAAAC	544	9795	GUUACUGGUAGGGC	2195
9795	CAGGUACUJGUCCUUAU	545	9795	CAGGUACUJGUCCUUAU	545	9813	AUAAGAGGCAAGAUACCUG	2196
9813	UAAACAAGUACAAAGUAUUC	546	9813	UAAACAAGUACAAAGUAUUC	546	9831	AAAAUACUJGUACUUGUUA	2197
9831	CAUGGGAGCCUJGUAGAU	547	9831	CAUGGGAGCCUJGUAGAU	547	9849	AGUAUCUAGGCCUCACUG	2198
9849	UACCAAGGUACUJGUAGGA	548	9849	UACCAAGGUACUJGUAGGA	548	9867	UGCUUACGUAGGGU	2199
9867	AGCUUJGUCCACUAGCA	549	9867	AGCUUJGUCCACUAGCA	549	9885	UGCUUACGUAGGGCAGAACGU	2200
9885	AAAGGGCUCUAAAAGACUUU	550	9885	AAAGGGCUCUAAAAGACUUU	550	9903	AAAGGUCAUJUAGGCCUUU	2201
9903	UAGCAACUCAGGUCCUGAU	551	9903	UAGCAACUCAGGUCCUGAU	551	9921	AUCAGGACCUJGUUGGUCA	2202
9921	UGUUCUCUACCAACCCA	552	9921	UGUUCUCUACCAACCCA	552	9939	UGGUUGGUAGGAGAACAA	2203
9939	ACAGACAUCAAUCACUICU	553	9939	ACAGACAUCAAUCACUUCU	553	9957	AGAAGUJGAAUJGUGUGUJ	2204
9957	UGCUGUJUCUGCAGGGU	554	9957	UGCUGUJUCUGCAGGGU	554	9975	ACCAJCUCUGCAGAACAGCA	2205
9975	UUUUAGGAAAAGGUUC	555	9975	UUUUAGGAAAAGGUUC	555	9993	GAUAGGCCAUUUUCCUAAA	2206
9993	CCCGUAGGCAAAGUCAA	556	9993	CCCGUAGGCAAAGUCAA	556	10011	UACUACUJGUACGCCG	2207
10011	AGGGUCAUGGUACAAAGUA	557	10011	AGGGUCAUGGUACAAAGUA	557	10029	UACUJGUACGUACGCCU	2208
10029	AACCUGGUAGGUACUACU	558	10029	AACCUGGUAGGUACUACU	558	10047	AGUJGUAGUUCACAGGU	2209
10047	UCUUAAGGUUJGGGUUG	559	10047	UCUUAAGGUUJGGGUUG	559	10065	CAACACAAUCCAUJAAAGA	2210
10065	GAUGGACACAGUACUJGU	560	10065	GAUGGACACAGUACUJGU	560	10083	ACAGUUAUCUGJGUCAUCC	2211
10083	UCCAAAGACAUJGUUJGC	561	10083	UCCAAAGACAUJGUUJGC	561	10101	GCAAAUJGACAUJGUUGGA	2212
10101	CACAGGAGAAAGACAUJGUU	562	10101	CACAGGAGAAAGACAUJGUU	562	10119	AAGGCAUGGUUCUGUGUG	2213
10119	UAAUCCUAAUCUAGGAAGAU	563	10119	UAAUCCUAAUCUAGGAAGAU	563	10137	AUCUUCUJGUAGUJAGGAUUA	2214
10137	UCUGCUCAUJCGCAAAUC	564	10137	UCUGCUCAUJCGCAAAUC	564	10155	GGAUJGUAGGAAAGCAGGA	2215
10155	CAACCAUAGCUUUCUJGUU	565	10155	CAACCAUAGCUUUCUJGUU	565	10173	AACAAAGAAAGGUAGGUUG	2216
10173	UCAGGGCGGCAAGUJGUAA	566	10173	UCAGGGCGGCAAGUJGUAA	566	10191	UUGGAAACAUJGUAGGCCUGA	2217
10191	ACUUUCGUGUUAUJGGCCAU	567	10191	ACUUUCGUGUUAUJGGCCAU	567	10209	AUGGCCAAUAAACAGGAAGU	2218
10209	UUCUAUGGAAAAGUJGUJGU	568	10209	UUCUAUGGAAAAGUJGUJGU	568	10227	CAGACAAUJUJGUCAUAGAA	2219
10227	GCUUAGGGCUUAAAUGGUAU	569	10227	GCUUAGGGCUUAAAUGGUAU	569	10245	AUCACUJUJAGGCCUAGC	2220
10245	UACUUUCUAAACCUAAAGACA	570	10245	UACUUUCUAAACCUAAAGACA	570	10263	UGUCUJGUAGGUUAAGUA	2221
10263	ACCCAAAGUAAAUIUJGU	571	10263	ACCCAAAGUAAAUIUJGU	571	10281	GACAAAUJUJACUJGU	2222
10281	CGCUAAUCCACCUJGUCAA	572	10281	CGCUAAUCCACCUJGUCAA	572	10299	UGACCCAGGUJGUAGGUACGG	2223
10289	AACAUUUUCAGUUCUAGCA	573	10299	AACAUUUUCAGUUCUAGCA	573	10317	UGCUJAGAACUJGUAGGU	2224
10317	AUGGUACAAUGGUUJGUACCA	574	10317	AUGGUACAAUGGUUJGUACCA	574	10335	UGGUJAGAACUJGUAGGU	2225
10335	AUCUGGUUJGUUJGUACGU	575	10335	AUCUGGUUJGUUJGUACGU	575	10353	ACACUGGUAAACACCGAGU	2226
10353	UGCCCAUGGAGACCUAAUCAU	576	10353	UGCCCAUGGAGACCUAAUCAU	576	10371	AUGAUUJAGGUUCUAGGU	2227
10371	UACCAUAAAAGGUUCUUC	577	10371	UACCAUAAAAGGUUCUUC	577	10389	GAAAGAACCUUJUJGUAGGU	2228
10389	CCUUAUGGAGAUCAUGGGU	578	10389	CCUUAUGGAGAUCAUGGGU	578	10407	ACCAUAGGUACUJGUAGGU	2229
10407	UAGGUUJGUUJGUUJACAUU	579	10407	UAGGUUJGUUJGUUJACAUU	579	10425	AAUGGUAAAACCAACACUJA	2230
10425	UGAUUUAUGGUUJGUUGGU	580	10425	UGAUUUAUGGUUJGUUGGU	580	10443	AGACACGGCAUJGUAGGU	2231
10443	UUUCUGGUUJGUUJGUACAU	581	10443	UUUCUGGUUJGUUJGUACAU	581	10461	AUGAUUJGUUJGUAGGUAAA	2232
10461	UAGGGAGCUUCCAAACAGGA	582	10461	UAGGGAGCUUCCAAACAGGA	582	10479	UCCUGUJGUAGGUAGGU	2233

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10479	AGUACACGCCGGGUACUGAC	583	10479	AGUACACGCCGGGUACUGAC	583	10497	GUAGUACACCAGCGGUACU	2234
10497	CUUAGAAGGGUAAUUCUAU	584	10497	CUUAGAAGGGUAAUUCUAU	584	10515	AUAGAAUUUACCUUCUAAAG	2235
10515	UGGUCCAUUUUGGUGAGAGA	585	10515	UGGUCCAUUUUGGUGACAGA	585	10533	UCUGUCAACAAUAGGACCA	2236
10533	ACAAACUGGCCAGGGUGCA	586	10533	ACAAACUGGCCAGGGUGCA	586	10551	UGCAGGCCUGUGCAGUUUGU	2237
10551	AGGUACAGACACAACCAUA	587	10551	AGGUACAGACACAACCAUA	587	10568	UAUGGUUGUGLICUGUACCU	2238
10569	ACAUUAAAUGUUUUUGGCA	588	10569	ACAUUAAAUGUUUUUGGCA	588	10587	UGCACAAAACAUUAAAUGUU	2239
10587	AUGGCUGUAUGCGUGCUUU	589	10587	AUGGCUGUAUGCGUGCUUU	589	10605	AACAGCAUGCAUACAGCCAU	2240
10605	UAUCAAUUGGGUGAUAGUGG	590	10605	UAUCAAUUGGGUGAUAGUGG	590	10623	CCACCUAGCAUACAUAGGAA	2241
10623	GUUCUCUUAAGAUUCACC	591	10623	GUUCUCUUAAGAUUCACC	591	10641	GGUGAAUUCUAAUAGAAAC	2242
10641	CACUACUUJUGAAUGACUU	592	10641	CACUACUUJUGAAUGACUU	592	10659	AAAGGUCAUUCAAAGUAGUG	2243
10659	UAACCUUJUGGGCAAAUGAAG	593	10659	UAACCUUJUGGGCAAAUGAAG	593	10677	CUUCAUUGGCCACAAGGUUA	2244
10677	GUACAACUAGAACCUCUUG	594	10677	GUACAACUAGAACCUCUUG	594	10695	CAAGGUCAUAGGUUGUAC	2245
10695	GACACAAGAUCAUGUUGAC	595	10695	GACACAAGAUCAUGUUGAC	595	10713	GUCAACAGAUCAUGUUGUC	2246
10713	CAUAUUGGGACCUCUUCU	596	10713	CAUAUUGGGACCUCUUCU	596	10731	AGAAAGAGGUCCCAAAUAG	2247
10731	UGCUCUAAACAGGAAUUGCC	597	10731	UGCUCUAAACAGGAAUUGCC	597	10749	GGCAAUUCUGUUGAGCA	2248
10749	CGUCUJAGAUAGUGUGCU	598	10749	CGUCUJAGAUAGUGUGCU	598	10767	AGCACACAUACUAAAGACG	2249
10767	UGCUUUJUGAAAGGCGUGCU	599	10767	UGCUUUJUGAAAGGCGUGCU	599	10785	CAGCAGGACUUCUAAAGCA	2250
10785	GCAGAAUUGGUAGAAUGGU	600	10785	GCAGAAUUGGUAGAAUGGU	600	10803	ACCAUUCUACAUUCUCG	2251
10803	UCGUACUCAUCCUUGGUAGC	601	10803	UCGUACUCAUCCUUGGUAGC	601	10821	GCUACCAAGGUAGUACGA	2252
10821	CACUAAUJUGAAAGAUGAG	602	10821	CACUAAUJUGAAAGAUGAG	602	10839	CUCAUCUUCUAAAUGUG	2253
10839	GUUJACACCAUJUGAUGUU	603	10839	GUUJACACCAUJUGAUGUU	603	10857	AACAUCAAGGUUGUAAAC	2254
10857	UGUJAGACAAUGCGUCUGGU	604	10857	UGUJAGACAAUGCGUCUGGU	604	10875	ACCGAGGACUUGGUUCUAAAC	2255
10875	UGUJACCUUCCAAGGUAG	605	10875	UGUJACCUUCCAAGGUAG	605	10893	CUUACCUUJGGAGGUAAACA	2256
10893	GUCAAGGAAUAGGUAG	606	10893	GUCAAGGAAUAGGUAG	606	10911	CUUACAUUJGUUCUUAAC	2257
10911	GGGCACUCAUCAUUGGAGA	607	10911	GGGCACUCAUCAUUGGAGA	607	10929	CAUCCAUAGGAGUGGCC	2258
10929	GUUUUUAACUUJUGGAGA	608	10929	GUUUUUAACUUJUGGAGA	608	10947	UGUCAAGAAAGGUAAAAGC	2259
10947	AUCACUAAUUGAUUUCGUU	609	10947	AUCACUAAUUGAUUUCGUU	609	10965	AACAGAAAUCAUAGUGAU	2260
10965	UCAAAGUACACAGUGGUCA	610	10965	UCAAAGUACACAGUGGUCA	610	10983	UGACCCACUGGUACUUUGA	2261
10983	ACUGUUUJUCUUUUUAC	611	10983	ACUGUUUJUCUUUUUAC	611	11001	GUAAAACAAAAGAACAGU	2262
11001	CGAGAAUGCCUUJUGGCA	612	11001	CGAGAAUGCCUUJUGGCA	612	11019	UGGCAAGAAAAGCAUUCUG	2263
11019	AUUACUCUJUGGUUAUAG	613	11019	AUUACUCUJUGGUUAUAG	613	11037	CAUAAUACCAAGGUAAA	2264
11037	GGCAAUUGCGCAUGGGCU	614	11037	GGCAAUUGCGCAUGGGCU	614	11055	AGCACACUGCGCAAUUGCC	2265
11055	UAUGCGUUCGUUAAGCAU	615	11055	UAUGCGUUCGUUAAGCAU	615	11073	AUGGUUAACAGUUGCAUA	2266
11073	UAAGGCACGCCAUUCUGGC	616	11073	UAAGGCACGCCAUUCUGGC	616	11091	GCACAGGAAAGGUUGGUUA	2267
11091	CUUGUUUJUGGUACCUUC	617	11091	CUUGUUUJUGGUACCUUC	617	11109	AGAAGGUAAAGGUAAAAG	2268
11109	UCUUGCAACAGUUGGUAC	618	11109	UCUUGCAACAGUUGGUAC	618	11127	GUAGCAACUGGUUGCAAGA	2269
11127	CUUAAAUGGUACUACAU	619	11127	CUUAAAUGGUACUACAU	619	11145	CAUGUAGCCAUUUAAAAG	2270
11145	GCCUGGUAGCGGGUGAUG	620	11145	GCCUGGUAGCGGGUGAUG	620	11163	CAUCACCCAGGUAGCAGGC	2271
11163	GGGUUAUCALIGACAUCCU	621	11163	GGGUUAUCALIGACAUCCU	621	11181	AAGCCAUJGUAGUACUGC	2272
11181	UGAAUUGGCCUGACACUAGC	622	11181	UGAAUUGGCCUGACACUAGC	622	11196	GCUAGUGUCAGCCAAUUC	2273
11199	CUUGUCUGGUUAAGGCCU	623	11199	CUUGUCUGGUUAAGGCCU	623	11217	AAGCCCUUAACAGACAAG	2274
11217	UAAGGUUGGUUAUGUAU	624	11217	UAAGGUUGGUUAUGUAU	624	11235	AUACAUAAACACAAUCCUUA	2275

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11235	UGCUUCAGGCUUAGUUUG	625	11235	UGCUUCAGGCUUAGUUUG	625	11253	CAAAACUAAAAGGUAGGCA	2276
11253	GCUUAUUCUCAUGACAGCU	626	11253	GCUUAUUCUCAUGACAGCU	626	11271	AGCJUGCUAGGAAUAGC	2277
11271	UCGGCACUGUUAGAUAGAU	627	11271	UCGGCACUGUUAGAUAGAU	627	11289	AUCAUCAUAAAAGGUGCGA	2278
11289	UGCUGCUAGACGGUUGG	628	11289	UGCUGCUAGACGGUUGG	628	11307	CCAAACAGGUCUAGGAGCA	2279
11307	GACACUGAUAGAAUGCUAU	629	11307	GACACUGAUAGAAUGCUAU	629	11325	AAUGACAUUCAUCAGUGUC	2280
11325	UACACUUGUUACAAAGUC	630	11325	UACACUUGUUACAAAGUC	630	11343	GACIUUGUAAAACAAGUGUA	2281
11343	CUACUAGGUAAAUGCUUA	631	11343	CUACUAGGUAAAUGCUUA	631	11361	UAAAGCAUJACAUAGUAG	2282
11361	AGAUCAAGCUAUUCCAU	632	11361	AGAUCAAGCUAUUCCAU	632	11379	CAUGGAAAAGCUUAGUACU	2283
11379	GAUGGGCCUUAQUUUAUICU	633	11379	GAUGGGCCUUAQUUUAUICU	633	11397	AGAAAUAAACUUAAGGCCAC	2284
11397	UGUAACCUCUACUACUACU	634	11397	UGUAACCUCUACUACUACU	634	11415	AGAAUAGUUAAGGGGUUACU	2285
11415	UGGGUGCUUACGACUAUC	635	11415	UGGGUGCUUACGACUAUC	635	11433	GAUAGUGCUAACGACACCA	2286
11433	CAUGUUUUUAGCUAGGCCU	636	11433	CAUGUUUUUAGCUAGGCCU	636	11451	AGCUCUAGCUAAAACAUG	2287
11451	UAUAGUGUUUAGUGUGUJU	637	11451	UAUAGUGUUUAGUGUGUJU	637	11469	AACACACACAAAACACUUA	2288
11469	UGAGUAUUAACCCAUUGUUA	638	11469	UGAGUAUUAACCCAUUGUUA	638	11487	UAAACAAUUGGGGUAAAUCUCA	2289
11487	AUUAUUAUGGGCAACACC	639	11487	AUUAUUAUGGGCAACACC	639	11505	GGUGUGGGCAAGUAAAUAU	2290
11505	CUUACAGGUUAUCAUCU	640	11505	CUUACAGGUUAUCAUCU	640	11523	AAGCAGAUACAGCUAGGAG	2291
11523	UGUUUAUIGGUUUCUAGGC	641	11523	UGUUUAUIGGUUUCUAGGC	641	11541	GCCUAAGAAAAGAAAUAACAA	2292
11541	CUAUUGUOUGCUGGUAC	642	11541	CUAUUGUOUGCUGGUAC	642	11559	GUAGCAGCAGCAACAAUAG	2293
11559	CUUUGGCCUUUCGUUUA	643	11559	CUUUGGCCUUUCGUUUA	643	11577	UAAACAGAAAAGGCCAAAG	2294
11577	ACUCAACCGUACUUCAGG	644	11577	ACUCAACCGUACUUCAGG	644	11595	CCUGAAGUAAAGGUUGAGU	2295
11595	GCUUACUCLUUGGGGUUUAU	645	11595	GCUUACUCLUUGGGGUUUAU	645	11613	AUAAACACCAAGGUAGGC	2296
11613	UGACUACUCLUUGGUUCUACA	646	11613	UGACUACUCLUUGGUUCUACA	646	11631	UGUAGAGACCAAGGUAGUCA	2297
11631	ACAAGAAUUAAGGUUAUG	647	11631	ACAAGAAUUAAGGUUAUG	647	11649	CAUAAUACCUAAAUCUUGU	2298
11649	GAACUCCCCAGGGGUUUG	648	11649	GAACUCCCCAGGGGUUUG	648	11667	CAAAAGCCCUGGGAGGUUC	2299
11667	GCCCUCCUAAGAGUAAU	649	11667	GCCCUCCUAAGAGUAAU	649	11685	AUAUACUACUJCUCUAGGAGGC	2300
11685	UGAUGCCLUUICAAGCUUAAC	650	11685	UGAUGCCLUUICAAGCUUAAC	650	11703	GUUJAGGJUUAAGGACAUCA	2301
11703	CAUUAAGGUUUGGGGUUU	651	11703	CAUUAAGGUUUGGGGUUU	651	11721	AAUACCCCAAACAAUCUUAUG	2302
11721	UGGAGGUAAACCAUGUAUC	652	11721	UGGAGGUAAACCAUGUAUC	652	11739	GAUACAGGUUUACCUCCA	2303
11739	CAAGGUUGGUACUGUACAG	653	11739	CAAGGUUGGUACUGUACAG	653	11757	CGUJACGUAGCAACCUUG	2304
11757	GUCAAAGGUUGGUACAGUA	654	11757	GUCAAAGGUUGGUACAGUA	654	11775	UACGUUGACAGUJJUAGAC	2305
11775	AAAGUGGCCACAUUCUGGUUA	655	11775	AAAGUGGCCACAUUCUGGUUA	655	11793	UACCCACAGAUGGGCACUUU	2306
11793	ACUGCUCUCGGGUUCUAA	656	11793	ACUGCUCUCGGGUUCUAA	656	11811	UUGGAAAGAACCGGAGGAGCU	2307
11811	ACAACUCAAGGUAGGUCA	657	11811	ACAACUCAAGGUAGGUCA	657	11829	UGACUCAUAAAUCUAGUUGU	2308
11829	AUCUUCUAAAUGGUUGGCA	658	11829	AUCUUCUAAAUGGUUGGCA	658	11847	UGCCCCACAUUJAGAAGAU	2309
11847	ACAAUGUGUACACUCCAC	659	11847	ACAAUGUGUACACUCCAC	659	11865	GUUGGAGUUGUACACAUUGU	2310
11865	CAAUGUAUUCUUCUUGCA	660	11865	CAAUGUAUUCUUCUUGCA	660	11883	UGCAAGAAAGAAUACAUUUG	2311
11883	AAAAGACACAAUCGAAAGCU	661	11883	AAAAGACACAAUCGAAAGCU	661	11901	AGCJUCAGGUUGUGCUUJU	2312
11901	UUUCGAGAAAGAUUGGUUCU	662	11901	UUUCGAGAAAGAUUGGUUCU	662	11919	AGAAACCAUCUUCUCGAAA	2313
11919	UCUUUUUGUUCGUUUUCUCA	663	11919	UCUUUUUGUUCGUUUUCUCA	663	11937	UAGGCAAAAGACAGACAAAAGA	2314
11937	AUCCAUUGCAGGGGUUCUGUA	664	11937	AUCCAUUGCAGGGGUUCUGUA	664	11955	UACAGGACCCUUGCAUGGGAU	2315
11955	AGACAUAAAUGGUUGGU	665	11955	AGACAUAAAUGGUUGGU	665	11973	GCACAAACCUUAAAUGGUCA	2316
11973	CGAGGAAAUGGUUCGUAAC	666	11973	CGAGGAAAUGGUUCGUAAC	666	11991	GUUAUCGAGCAUUUCUCG	2317

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11991	CCGUGCUACUCUUCAGGCCU	667	11991	CCGUGCUACUCUUCAGGCCU	667	12009	AGCCUGAAGGUAGGACGG	2318
12009	UAUUGCUCUCAAGAAUJAGU	668	12009	UAUUGCUCUCAAGAAUJAGU	668	12027	ACUAAAUCUGGAAAGCAAUA	2319
12027	UUCUUUUCAUCAUAGGCC	669	12027	UUCUUUUCAUCAUAGGCC	669	12045	GGAUUAUGGUAAAAGAA	2320
12045	CGCUUAUGCCACUGCCAG	670	12045	CGCUUAUGCCACUGCCAG	670	12063	CUGGGCAGUGGCAUAAGCG	2321
12063	GGAGGCCUAUGGAGGGCU	671	12063	GGAGGCCUAUGGAGGGCU	671	12081	AGCCUGCUACUAGGCCUC	2322
12081	UGUAGCUAAUGGUGAUUCU	672	12081	UGUAGCUAAUGGUGAUUCU	672	12099	AGAAUCACCAUAGGACUACA	2323
12099	UGAAGGUCCUUCUCAAAAG	673	12099	UGAAGGUCCUUCUCAAAAG	673	12117	CUUUUGAGAACGACUUCUCA	2324
12117	GUUAAAAGAAUUCUUGGAAU	674	12117	GUUAAAAGAAUUCUUGGAAU	674	12135	AUUCAAAAGAUUUCUUAAC	2325
12135	UGGGCUAAAUCUGAGGUU	675	12135	UGGGCUAAAUCUGAGGUU	675	12153	AAACUCAGAUUAGGCCACA	2326
12153	UGACCGUGCUGCAUG	676	12153	UGACCGUGCUGCCAUAG	676	12171	CAUGGCAGCACAGGGGUCA	2327
12171	GCAACGCCAUGGGAAAG	677	12171	GCAACGCCAUGGGAAAG	677	12189	CUUUUCCAACIUGGGUUGC	2328
12189	GAUGGCCAGAUACGGCUAUG	678	12189	GAUGGCCAGAUACGGCUAUG	678	12207	CAUAGCCUGCAUCUGGCCAUC	2329
12207	GACCCAAAGUACAAACAG	679	12207	GACCCAAAGUACAAACAG	679	12225	CUGGUUQUACAUUJGGGUUC	2330
12225	GGCAAGAUUCUGAGGACAAG	680	12225	GGCAAGAUUCUGAGGACAAG	680	12243	CUUGGUCCUCAUCUUGGCCUC	2331
12243	GAGGGCAAAAGUAAUCAUGU	681	12243	GAGGGCAAAAGUAAUCAUGU	681	12261	ACUAGGUUACUUIUUGGCCUC	2332
12261	UGCUCUAUGCCAAACAUUGCUC	682	12261	UGCUCUAUGCCAAACAUUGCUC	682	12279	GAGCAUUGGUUIGCAUAGCA	2333
12279	CUUCACUACUAGCUUAGGAAG	683	12279	CUUCACUACUAGCUUAGGAAG	683	12297	CUUCCUAGCAUAGUGAAG	2334
12297	GUUJGUAUAGAUGCAUU	684	12297	GUUJGUAUAGAUGCAUU	684	12315	AAUGGCAUCAUUACUAGC	2335
12315	UACACACAUAAUCAAAU	685	12315	UACACACAUAAUCAAAU	685	12333	AUUGGUUGAUAAUGGUUGUA	2336
12333	UGCGCGUGAUGGUUGGUU	686	12333	UGCGCGUGAUGGUUGGUU	686	12351	AACACAACCAUCACGGC	2337
12351	UCCACACUAAACAUAAUCCA	687	12351	UCCACACUAAACAUAAUCCA	687	12369	UGGUAGAUGUUGAGGUUGA	2338
12369	AUUGACUACAGCGCCAA	688	12369	AUUGACUACAGCGCCAA	688	12387	UUUGGUGGUUGGUUGUCAAU	2339
12387	ACUCAUGGUUGGUCCCCU	689	12387	ACUCAUGGUUGGUCCCCU	689	12405	AGGGACAACAAACAUAGAU	2340
12405	UGAUUUAUGGUACCUACAAAG	690	12405	UGAUUUAUGGUACCUACAAAG	690	12423	CUUGGUAGUACCAUAUCA	2341
12423	GAACACUJUGUGAUGGUAAAC	691	12423	GAACACUJUGUGAUGGUAAAC	691	12441	GUUACCAUCACAGGUUC	2342
12441	CACCUUACAUAGCAUCU	692	12441	CACCUUACAUAGCAUCU	692	12459	AGAUGCAUAGUAAAAGUG	2343
12459	UGCAACUCUGGGAAAUCAG	693	12459	UGCAACUCUGGGAAAUCAG	693	12477	CUGGAAUUCAGAGUGCA	2344
12477	GCAAGUUGGUAGGGAU	694	12477	GCAAGUUGGUAGGGAU	694	12495	AUCCGCAUCACAAACUUC	2345
12495	UAGCAAGAUUGGUACCUACUU	695	12495	UAGCAAGAUUGGUACCUACUU	695	12513	AAGUUGAACAAUCUUC	2346
12513	UAGUGAAAUAACAUAGGAC	696	12513	UAGUGAAAUAACAUAGGAC	696	12531	GUCAUUAUUCUACAUUA	2347
12531	CAAUUCACAAUJUGGCCU	697	12531	CAAUUCACAAUJUGGCCU	697	12549	AGCAAAUUUUGGUAGAUUG	2348
12549	UUGGCCUCUAAUUGGUACA	698	12549	UUGGCCUCUAAUUGGUACA	698	12567	UGUAAAUAAGGGCCAA	2349
12567	AGCCUCUAAAGAGGCCAACU	699	12567	AGCCUCUAAAGAGGCCAACU	699	12585	UGAGUUGGUUCUAGAGCU	2350
12585	AGCUGUUAACAUAGGAAU	700	12585	AGCUGUUAACAUAGGAAU	700	12603	AUJCUGUAGUUAACAGCU	2351
12603	UAAUGAACUGAGGUCCAGUA	701	12603	UAAUGAACUGAGGUCCAGUA	701	12621	UACUGGACUCAGGUCAUA	2352
12621	AGCACUACAGAGGUCC	702	12621	AGCACUACAGAGGUCC	702	12639	GGACACUCAGCAGGUUGCU	2353
12639	CUGUGCGGCGGUACCAC	703	12639	CUGUGCGGCGGUACCAC	703	12657	UGUGGUACCAAGCCGACAG	2354
12657	ACAAACAGCUUJUGGUACAU	704	12657	ACAAACAGCUUJUGGUACAU	704	12675	AUCAGUACAAGCUGUUUGU	2355
12675	UGACAAUGGACAUJUGCCUAC	705	12675	UGACAAUGGACAUJUGCCUAC	705	12693	GUAGGCAAGUGCAUUGUCA	2356
12693	CUAAACAAUUCGAAGGG	706	12693	CUAAACAAUUCGAAGGG	706	12711	UCCCUUCGAAUUGGUUAAG	2357
12711	AGGUAGGUUGGUUGGGCA	707	12711	AGGUAGGUUGGUUGGGCA	707	12729	UGCCAGCACAAACCUACCU	2358
12729	AUUACUAUCAGACCAACAA	708	12729	AUUACUAUCAGACCAACAA	708	12747	UGGGGGCUCUGAUAGUAAU	2359

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12747	AGAUCUCAAAUGGGCUAGA	709	12747	AGAUCUCAAAUGGGCUAGA	709	12765	UCUAGCCAUUUGAGAUUCU	2360
12765	AUUCCCUAAGAGUGGU	710	12765	AUUCCCUAAGAGUGGU	710	12783	ACCAUCACUCUUAAGGGAAU	2361
12783	UACAGGUACAAUUCACAA	711	12783	UACAGGUACAAUUCACAA	711	12801	UGUGAAAUGGUACCUGUA	2362
12801	AGAACUCCGGAACCCUUUGU	712	12801	AGAACUCCGGAACCCUUUGU	712	12819	ACAAGGGGUAGGUACGUUCU	2363
12819	UAGGUUUUGUACAGACACA	713	12819	UAGGUUUUGUACAGACACA	713	12837	UGUGGUAGGUACAAACCUA	2364
12837	ACCAAAAGGGCCUAAAGUG	714	12837	ACCAAAAGGGCCUAAAGUG	714	12855	CACUUUAGGCCCUUUGGU	2365
12855	GAAAUCUGUACUUCACU	715	12855	GAAAUCUGUACUUCACU	715	12873	GAUGAAGUACAGUAAUUC	2366
12873	CAAAGGCUAAAACCUA	716	12873	CAAAGGCUAAAACCUA	716	12891	UAGGUUUUAGCCUUUG	2367
12891	AAAUAAGGGUAUGGGCUG	717	12891	AAAUAAGGGUAUGGGCUG	717	12909	CAGGACCAUACUCUAAUUU	2368
12909	GGGCAGUUUAGCUCUACA	718	12909	GGGCAGUUUAGCUCUACA	718	12927	UGUAGCAGCUAAACUGCCC	2369
12927	AGUACGUUCUUCAGGCCUG	719	12927	AGUACGUUCUUCAGGCCUG	719	12945	UCCAGGCCUGAAACGUACU	2370
12945	AAAUGGUACAGAAGGUCCU	720	12945	AAAUGGUACAGAAGGUCCU	720	12963	AGGUACUUCUGUAGGCAUU	2371
12963	UGCCAAAUCUACUGGUU	721	12963	UGCCAAAUCUACUGGUU	721	12981	AAGCAGUUGGAAUUGGCA	2372
12981	UICCCUUCUGGUUUCGCA	722	12981	UICCCUUCUGGUUUCGCA	722	12999	UGCCAAAAGGAGGAAAGAA	2373
12999	AGUAGACCCUGCUAAAGCA	723	12999	AGUAGACCCUGCUAAAGCA	723	13017	UGCCUUUAGGCGGUUCUACU	2374
13017	AUAUAAGGUUACCUAGCA	724	13017	AUAUAAGGUUACCUAGCA	724	13035	UGCCUAGGUAAUCCUUAU	2375
13035	AAGUGGGAGGACAACCAUC	725	13035	AAGUGGGAGGACAACCAUC	725	13053	GAUJGGGUUGGUCCUCCACU	2376
13053	CACCAACUGUGUAAGAUG	726	13053	CACCAACUGUGUAAGAUG	726	13071	CAUCUUCACAGUUGGGUG	2377
13071	GUIGUGUACACACACUGGU	727	13071	GUIGUGUACACACACUGGU	727	13089	ACCGAGUGUGUGUACACAAC	2378
13089	UACAGGAGACAGGCAAAUACU	728	13089	UACAGGAGACAGGCAAAUACU	728	13107	AGUAAAUGGCCUGGUCCUGUA	2379
13107	UGUAAACACCAGGUACUAC	729	13107	UGUAAACACCAGGUACUAC	729	13125	GUUAGCUCUCCGGGUUACU	2380
13125	CAUGGACCAAGAGGUUU	730	13125	CAUGGACCAAGAGGUUU	730	13143	AAAGGACUUGGUUGGUCCAU	2381
13143	UGGUGGGUGGUCAUGUJGU	731	13143	UGGUGGGUGGUCAUGUJGU	731	13161	ACAAACAUAGAACCCACCA	2382
13161	UCUGUAUUGGUAGUGCAC	732	13161	UCUGUAUUGGUAGUGCAC	732	13179	GUGGCAUCUACAAUACAGA	2383
13179	CAUUGACCAUCCAAAUCU	733	13179	CAUUGACCAUCCAAAUCU	733	13197	AGGAUJJGGAUUGGUCAUG	2384
13197	AAAAGGAUUCUUCGUACUUG	734	13197	AAAAGGAUUCUUCGUACUUG	734	13215	CAAGGUACAGAAUCCUUUA	2385
13215	GAAAGGUAAAGUACGUCAA	735	13215	GAAAGGUAAAGUACGUCAA	735	13233	UIGGACGUACUACCUUUC	2386
13233	AUACCUCACCUUCUGGU	736	13233	AUACCUCACCUUCUGGU	736	13251	AGCCAACAGGUUGGUAAU	2387
13251	UAAUGACCCGGGUUU	737	13251	UAAUGACCCGGGUUU	737	13269	AAAACCCACUCCGGGUAAU	2388
13269	UACACUUAAGAACACAGUC	738	13269	UACACUUAAGAACACAGUC	738	13287	GACUUCGGAGACGGGUACAG	2389
13287	CUGUACCGUUCGGGGAAUG	739	13287	CUGUACCGUUCGGGGAAUG	739	13305	CAUCUCCGAAACCUUUCAC	2390
13305	GUGGAAAAGGUUAGGUUGU	740	13305	GUGGAAAAGGUUAGGUUGU	740	13323	ACAGCCAUAAACCUUAAA	2391
13323	UAGGUUGGUACCAACUCGC	741	13323	UAGGUUGGUACCAACUCGC	741	13341	GGGGAGUUGGUACACAAU	2392
13341	CGAACCCUUGAUGCAGUC	742	13341	CGAACCCUUGAUGCAGUC	742	13359	AGACUGCAUCAGGGGUUG	2393
13359	UGCGGAUGCAGCAACGUU	743	13359	UGCGGAUGCAGCAACGUU	743	13377	AAACGUUGAUGCACCGCA	2394
13377	UUUAAAACGGGUUUGGGUG	744	13377	UUUAAAACGGGUUUGGGUG	744	13395	CACCGGAAACCCGUUAAA	2395
13395	GUAGUGGAGGCCGUUUA	745	13395	GUAGUGGAGGCCGUUUA	745	13413	UAAGGACGGGGUGCCACUAC	2396
13413	ACACCGUGGGCACAGGCA	746	13413	ACACCGUGGGCACAGGCA	746	13431	UGCCUGUGGCCACGGGU	2397
13431	ACUAGUACUAGUAGUCGU	747	13431	ACUAGUACUAGUAGUCGU	747	13449	AGACGAGAUCAUGUACUAG	2398
13449	UACAGGGCUUUUJGUAIUU	748	13449	UACAGGGCUUUUJGUAIUU	748	13467	AAAUAUCAAAAAGCCUGUA	2399
13467	UACAACGAAAAAGGUUGCUG	749	13467	UACAACGAAAAAGGUUGCUG	749	13485	CAGGAAUCUUUJGUUGUUA	2400
13485	GUUUUUGCAAAGGUCCUAA	750	13485	GUUUUUGCAAAGGUCCUAA	750	13503	UAGGAAUCUUUJGUUGUUA	2401

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13503	AAAACUAAUUGCGGCCU	751	13503	AAAACUAAUUGCGGCCU	751	13521	AGGGACAGCAGCAAUUAGUUUU	2402
13521	UCCAGGAGAAGGAUGAGG	752	13521	UCCAGGAGAAGGAUGAGG	752	13539	CCUCAUCCUUCUCCUGGAA	2403
13539	GAAGGCAAUUUUAGACU	753	13539	GAAGGCAAUUUUAGACU	753	13557	AGUCUAUAAAUGCCUUC	2404
13557	UCUUAUCUUGUAGUAGA	754	13557	UCUUAUCUUGUAGUAGA	754	13575	UCUUAUCUACAAAGUAAGA	2405
13575	AGGCAUACUAUGCUAACU	755	13575	AGGCAUACUAUGCUAACU	755	13593	AGUJAGACAUAGUAUGCCU	2406
13593	UACCAACAUGAAGACUA	756	13593	UACCAACAUGAAGACUA	756	13611	UAGUCUCUCAUGUUGGUA	2407
13611	AUUUAUACUUGGUAAAAG	757	13611	AUUUAUACUUGGUAAAAG	757	13629	CJJUUAACCAAGUUAUAAA	2408
13629	GAUUUGCCAGGGGUUGUG	758	13629	GAUUUGCCAGGGGUUGUG	758	13647	CAGGAAACGGUGGACAAUC	2409
13647	GUCCAUGACUUUUCAAGU	759	13647	GUCCAUGACUUUUCAAGU	759	13665	ACUIGAAAAAGUCAUGGAC	2410
13665	UUUAGAGUAGAUGGGAGCA	760	13665	UUUAGAGUAGAUGGGAGCA	760	13683	UGUCACCAUCUACUCAA	2411
13683	AUGGUACCACAUAUAC	761	13683	AUGGUACCACAUAUAC	761	13701	GUGAUUAUAGGUUACCAU	2412
13701	GUCAAGCGLCUAACUAAU	762	13701	GUCAAGCGLCUAACUAAU	762	13719	AUJUAGUUAAGCGUGACG	2413
13719	UACACAAUGGCUGAUUAG	763	13719	UACACAAUGGCUGAUUAG	763	13737	CJAAUACAGCCAUUGUGUA	2414
13737	GUICUAUGCUACGUCAU	764	13737	GUICUAUGCUACGUCAU	764	13755	AAUGACGUAGGCAUAGAC	2415
13755	UUUGAUGAGGGGUAAAUG	765	13755	UUUGAUGAGGGGUAAAUG	765	13773	CACAAUUAACCCUCAUAAA	2416
13773	GAUACAUAAAAGAAUAC	766	13773	GAUACAUAAAAGAAUAC	766	13791	GUAAUJUUAUAAAUGUAUC	2417
13791	CUCGUACACAUAAUUGCU	767	13791	CUCGUACACAUAAUUGCU	767	13809	AGCJAUJUUAUUGUGGAG	2418
13809	UGUGAUGAGUAAUUCU	768	13809	UGUGAUGAGUAAUUCU	768	13827	UGAAUAAUUCUACUACACA	2419
13827	AUUAAGAAGGAGUUGGUAG	769	13827	AUUAAGAAGGAGUUGGUAG	769	13845	CAUACCAAUCUUCUUAUU	2420
13845	GACUUUCGUAGGAAUCUG	770	13845	GACUUUCGUAGGAAUCUG	770	13863	CAGGAUUCUACGAAGUC	2421
13863	GACAUCUACCGGUAAUG	771	13863	GACAUCUACCGGUAAUG	771	13881	CAUAAUACCGGUAAAGUC	2422
13881	GCUAACUAGGUGAGCUG	772	13881	GCUAACUAGGUGAGCUG	772	13899	CACGCCUACCUAAGUAGC	2423
13899	GUACGCCAACUAAUUA	773	13899	GUACGCCAACUAAUUA	773	13917	UJAAUAAUAGUJUUGGUAC	2424
13917	AAGACUGUACAAUUCUG	774	13917	AAGACUGUACAAUUCUG	774	13935	CGGAGAAUUGGUACAGUCU	2425
13935	GAUGCUAUGCAGGGGUAG	775	13935	GAUGCUAUGCAGGGGUAG	775	13953	CGUGAUACCGCAUAGCAUC	2426
13953	GCACAUUGAGGGGUAGU	776	13953	GCACAUUGAGGGGUAGU	776	13971	UCAJGJACGCCAUAGUCC	2427
13971	ACAUUAGAUAAUCAGGAU	777	13971	ACAUUAGAUAAUCAGGAU	777	13989	GAUCCUGAUUAUCAUAAUGU	2428
13989	CJUAAUGGGAACUGGUAG	778	13989	CJUAAUGGGAACUGGUAG	778	14007	CGUACCAUGUCCCAUUAAG	2429
14007	GAUUCGGGUAUUCGUAC	779	14007	GAUUCGGGUAUUCGUAC	779	14025	GUACGAAAUCACCGAAAUC	2430
14025	CAAGUAGGCCAGCGUGCG	780	14025	CAAGUAGGCCAGCGUGCG	780	14043	CGCACGCCUGGUCCUACUUG	2431
14043	GGAGUUCUAUUGGGAUU	781	14043	GGAGUUCUAUUGGGAUU	781	14061	AAUCACAAUAGGAAACUCC	2432
14061	UCAUAAUACUACUUGUGA	782	14061	UCAUAAUACUACUUGUGA	782	14079	UCAGGCAAUUGGUAAUAGA	2433
14079	AUGCCCAUCUCCACUUGA	783	14079	AUGCCCAUCUCCACUUGA	783	14097	UCAAAUGGAGGAUGGGCAU	2434
14097	ACUAGGGCAUUGGCCUG	784	14097	ACUAGGGCAUUGGCCUG	784	14115	CAGGACGCCAACUCCUAGU	2435
14115	GAGUCCCAUAGGGAUGCUG	785	14115	GAGUCCCAUAGGGAUGCUG	785	14133	CAGGACGCCAACUCCUAGU	2436
14133	GAUCUCGCCAAACACUUA	786	14133	GAUCUCGCCAAACACUUA	786	14151	UAGGUUGGUUUUGGAGAUUC	2437
14151	AUUAAGUGGGAUUUGCUGA	787	14151	AUUAAGUGGGAUUUGCUGA	787	14169	UCAGGAAUACCCACUUAUU	2438
14169	AAAUAUGAUUUUACGGAA	788	14169	AAAUAUGAUUUUACGGAA	788	14187	CJUCCGUAAAUCAUUU	2439
14187	GAGAGACUUGUCUCUUCG	789	14187	GAGAGACUUGUCUCUUCG	789	14205	CGAAGAGACAAGUCUC	2440
14205	GACCGGUAUUUUAAAUAU	790	14205	GACCGGUAUUUUAAAUAU	790	14223	AAUAUUAAAUAACGGUC	2441
14223	UGGGACAGACAUACCAUC	791	14223	UGGGACAGACAUACCAUC	791	14241	GAUUCGUAGUGUCUGGUCCCA	2442
14241	CCCCAAUUGUAAUACUGUU	792	14241	CCCCAAUUGUAAUACUGUU	792	14259	AACAGUUAUACAAUUGGG	2443

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14259	UUGGAUGAUAGGGGUUAUCC	793	14259	UUGGAUGAUAGGGGUUAUCC	793	14277	GGAUACACCJAUCAUCCAA	2444
14277	CUUCAUUGGCAAAACIUUUA	794	14277	CUUCAUUGGCAAAACIUUUA	794	14295	UAAAGUUUUGGCCAACUAGG	2445
14295	A AUGGUUAUUUUCUACGU	795	14295	A AUGGUUAUUUUCUACGU	795	14313	CAGUAGAAAAAUAAACACAUU	2446
14313	GUGUUUCCACCUJACAGU	796	14313	GUGUUUCCACCUJACAGU	796	14331	AACUUGUAGGUGGAAAACAC	2447
14331	UUUGGACCAACUAGUAAGAA	797	14331	UUUGGACCAACUAGUAAGAA	797	14349	UUCUACUAGGUUGGUCCAAA	2448
14349	AAAUAUUUUGUAGAUGGUG	798	14349	AAAUAUUUUGUAGAUGGUG	798	14367	CACCAUCUACAAUAAUJJU	2449
14367	GUUCUUUUGGUUUCUCAA	799	14367	GUUCUUUUGGUUUCUCAA	799	14385	UUGAAAACAACAAAAGGAAC	2450
14385	ACUGGAUACCAUUUCGGUG	800	14385	ACUGGAUACCAUUUCGGUG	800	14403	CACGAAAAUGGJAUCCAGU	2451
14403	GAGUUAGGAGGUICGUACUA	801	14403	GAGUUAGGAGGUICGUACUA	801	14421	UAUGUACGACUCCUAAUC	2452
14421	AAUCAGGAUGGUAAACUAC	802	14421	AAUCAGGAUGGUAAACUAC	802	14439	GUAGGUUACAUCCUGAU	2453
14439	CAUAGCUCGCGGUUCAGUU	803	14439	CAUAGCUCGCGGUUCAGUU	803	14457	AACUGAGACGGGAGCUAU	2454
14457	UUCAAGGAACGUUUCAGUU	804	14457	UUCAAGGAACGUUUCAGUU	804	14475	ACACUAAAAGGUUCUJUGAA	2455
14475	UAUGCUGCUGGUACCGCUA	805	14475	UAUGCUGCUGGUACCGCUA	805	14493	UAGCUGGUAGGAGCAGCAU	2456
14493	AUGCAUGCAGGUUCUGGCA	806	14493	AUGCAUGCAGGUUCUGGCA	806	14511	UGCCAGAAAGCUCAGCAU	2457
14511	AAUUUAUUGGUAGAUAAAC	807	14511	AAUUUAUUGGUAGAUAAAC	807	14529	GUUUAUCUAGGAAUAAAUU	2458
14529	CGCACUACAUAGGUUCUUCAG	808	14529	CGCACUACAUAGGUUCUUCAG	808	14547	CUGAAAAGCAUGGUAGUGCG	2459
14547	GUAGCUGGCACUAAACAAACA	809	14547	GUAGCUGGCACUAAACAAACA	809	14565	UGUUUAGUAGGAGCUAC	2460
14565	AAUGGUUGGUUUUCAACUG	810	14565	AAUGGUUGGUUUUCAACUG	810	14583	CAGUUUAGGAAACAUU	2461
14583	GUCAAACCCGGGUUUUUA	811	14583	GUCAAACCCGGGUUUUUA	811	14601	UAAAUUUACCGGGUUGAC	2462
14601	AAUAAAAGACGUUUUAGACU	812	14601	AAUAAAAGACGUUUUAGACU	812	14619	AGUCUAAAAGGUUUAU	2463
14619	UUUGCUGGUUCGUAAAAGUU	813	14619	UUUGCUGGUUCGUAAAAGUU	813	14637	AACCUUUAGACACAGCAA	2464
14637	UUUUUUAGGAAGGAAGGUU	814	14637	UUUUUUAGGAAGGAAGGUU	814	14653	AACCUUUAGGUUUAAGAA	2465
14655	UCUGGUUGGUACUAAACACU	815	14655	UCUGGUUGGUACUAAACACU	815	14673	AGGUUUGGUAGGUAGGAA	2466
14673	UUCUUCUUUGGUAGGAUG	816	14673	UUCUUCUUUGGUAGGAUG	816	14691	CAUCCUGAGGAGGUAGGAA	2467
14691	GIGCAACGGGUUCUACAGUG	817	14691	GIGCAACGGGUUCUACAGUG	817	14709	CACUGAUAGGAGCUGUUGGC	2468
14709	GAUUAUGACUUAUACGUU	818	14709	GAUUAUGACUUAUACGUU	818	14727	AACGAAUAAUGGUCAUAAUC	2469
14727	UAUAAUCUGCCACAAAGU	819	14727	UAUAAUCUGCCACAAAGU	819	14745	ACAUUUGGGAGGUUUA	2470
14745	UGUGAUUAUCAGACAUCC	820	14745	UGUGAUUAUCAGACAUCC	820	14763	GGAGGUUGGUUGGUAGCA	2471
14763	CUAUUUCGGGUUGGUAGGU	821	14763	CUAUUUCGGGUUGGUAGGU	821	14781	CAACUUCUACUACGAAUAG	2472
14781	GUIGUAAAUAUACUJUGAUU	822	14781	GUIGUAAAUAUACUJUGAUU	822	14799	AAUCAAAAGGUUUAUACAC	2473
14799	UGUUCAGCAUGGGCJGUUA	823	14799	UGUUCAGCAUGGGCJGUUA	823	14817	UACAGCCACCAUCGUUAAA	2474
14817	AUAAAUGCCAAACGUAA	824	14817	AUAAAUGCCAAACGUAA	824	14835	UUAUCUUGGUUGGUCAUUA	2475
14835	AUCGUUACAAUCUGGUAA	825	14835	AUCGUUACAAUCUGGUAA	825	14853	UAUCCAGAUJUGGUUACG	2476
14853	AAAUCAGCJGGGUUCUCCAU	826	14853	AAAUCAGCJGGGUUCUCCAU	826	14871	AUGGGAAAACCGCUGAUU	2477
14871	UUUUUUAAAUGGGGUAGG	827	14871	UUUUUUAAAUGGGGUAGG	827	14889	CCUUUACCCCAUUUUAAA	2478
14889	GCUAGACUUAUUAUGACU	828	14889	GCUAGACUUAUUAUGACU	828	14907	AGCUAAUAAAUGCUAGC	2479
14907	UCAAUGGUAGGUAGGAUC	829	14907	UCAAUGGUAGGUAGGAUC	829	14925	GAUCCUCUAAACCUAU	2480
14925	CAAGAUGGCACUJJUUCGGU	830	14925	CAAGAUGGCACUJJUUCGGU	830	14943	ACCGGAAAAGGUCAUUG	2481
14943	UUAUACUAAAGCJGUUAJGU	831	14943	UUAUACUAAAGCJGUUAJGU	831	14961	UGACAUJACGGGUUAGUA	2482
14961	AUCCCUACUUAACUJCACAA	832	14961	AUCCCUACUUAACUJCACAA	832	14979	UUJAGGUUAUGGUAGG	2483
14979	AUGAAUCUUAAGUAGGCCA	833	14979	AUGAAUCUUAAGUAGGCCA	833	14997	UGGCAUACUUAAGAUCAU	2484
14997	AUUAUGGGCAAAAGAUAGAG	834	14997	AUUAUGGGCAAAAGAUAGAG	834	15015	CUCUJAUUCUJUGGUCAU	2485

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15015	GCUCGCACCGUAGCGGUG	835	15015	GCUCGCCACCGUAGCGGUG	835	15033	CACCAAGCJACGGGUUGCGAGC	2486
15033	GUUCUCUAUCUGUAGGUACUA	836	15033	GUUCUCUAUCUGUAGGUACUA	836	15051	UAGGUACUACAGAUAGAGAC	2487
15051	AUGACAAAUAUGACAGUUUC	837	15051	AUGACAAAUAUGACAGUUUC	837	15069	GAAACUGUCUAAUUGGUCAU	2488
15069	CAUCAGAAAAUUAUUGAAGU	838	15069	CAUCAGAAAAUUAUUGAAGU	838	15087	ACUUCAAUAAAUCUCUGAUG	2489
15087	UCAUAAUAGCCGCCACUAGAG	839	15087	UCAUAAUAGCCGCCACUAGAG	839	15105	CUCUAGGGCCGUAAUUGA	2490
15105	GGAGCUACUGUGGUUAUUG	840	15105	GGAGCUACUGUGGUUAUUG	840	15123	CAAUUACCAAGGUAGGUCC	2491
15123	GGAAACAAGCAAGUUUAUCG	841	15123	GGAAACAAGCAAGUUUAUCG	841	15141	CGUAAAACUUGGUUGUUC	2492
15141	GGGGCGGGCAUAAUAGU	842	15141	GGGGCGGGCAUAAUAGU	842	15159	ACAUUUAAUGCAGGCCACC	2493
15159	UAAAACUACGUUUACAGUG	843	15159	UAAAACUACGUUUACAGUG	843	15177	CACGUAAAAGGUUUUAA	2494
15177	GAUGUAGAAAACUCCACCC	844	15177	GAUGUAGAAAACUCCACCC	844	15195	GGUGUGGAGGUUCUACAU	2495
15195	CUUAGGGGUUGGGGAUUAUC	845	15195	CUUAGGGGUUGGGGAUUAUC	845	15213	GAUAAAUCCCAACCCAUAAAG	2496
15213	CCAAAUGUGACAGGCCA	846	15213	CCAAAUGUGACAGGCCA	846	15231	UGGCUCUGUCACAUUUUG	2497
15231	AUGCCUACACUAGGUAGGA	847	15231	AUGCCUACACUAGGUAGGA	847	15249	UCCUAGCAUUGGGCAU	2498
15249	AUAAUAGGCCACUCUUGUIC	848	15249	AUAAUAGGCCACUCUUGUIC	848	15267	GAACAAAGGAGGCCAUAU	2499
15267	CUUGCUCUCGAAACAUACA	849	15267	CUUGCUCUCGAAACAUACA	849	15285	UGUUAUAGUUUCCGAGCAA	2500
15285	ACUUGCGUACUUAUCAC	850	15285	ACUUGCGUACUUAUCAC	850	15303	GUGUAAGGUUACAGCAAGU	2501
15303	CAACGUUUUCUACGGUAG	851	15303	CAACGUUUUCUACGGUAG	851	15321	CUAACGUUAGAAACGGUG	2502
15321	GCUAACGGAGUGGGCGAAG	852	15321	GCUAACGGAGUGGGCGAAG	852	15339	CUUGGCACACUGGUAGGC	2503
15339	GUAAUUAAGUGAGAUUGUCA	853	15339	GUAAUUAAGUGAGAUUGUCA	853	15357	UGACCAUCUACUUAUAC	2504
15357	AUGUGUGGGGGCUACUAU	854	15357	AUGUGUGGGGGCUACUAU	854	15375	AUAGUGAGGCCACACAU	2505
15375	UAUGUUAAAACCGGGGAA	855	15375	UAUGUUAAAACCGGGGAA	855	15393	UUCACCUUGGUUAACAU	2506
15393	ACAUCAUCGGGUAGAUAG	856	15393	ACAUCAUCGGGUAGAUAG	856	15411	UAGCAUCACCGGAUGU	2507
15411	ACAACUGCUUAUAGCUAU	857	15411	ACAACUGCUUAUAGCUAU	857	15429	UAUUAGGUAAUAGGUUGU	2508
15429	AGUGUCUUAACUUUGUC	858	15429	AGUGUCUUAACUUUGUC	858	15447	GACAAAAGGUUAAGACACU	2509
15447	CAAGCGUACAGCCAAUG	859	15447	CAAGCGUACAGCCAAUG	859	15465	CAUJGGCUGUACACGGUUG	2510
15465	GUAAAUGCACUUCUUCUAA	860	15465	GUAAAUGCACUUCUUCUAA	860	15483	UUGAAAAGGUCAUUAUC	2511
15483	ACUGAUGGUAAAAGAUAG	861	15483	ACUGAUGGUAAAAGAUAG	861	15501	CUACUUCUAAUACCAUCAGU	2512
15501	GCUGACAAAGUAGUCCGCA	862	15501	GCUGACAAAGUAGUCCGCA	862	15519	UGCGGACAUACUUGUICAGC	2513
15519	AUCUACAAACAGGCUU	863	15519	AUCUACAAACAGGCUU	863	15537	AGAGCCUGUGUUGUAGAU	2514
15537	UAUGAGUGUCUUCUAGAA	864	15537	UAUGAGUGUCUUCUAGAA	864	15555	UUCUUAAGACACUCUAA	2515
15555	AUAAGGGAGGUAGUAGAU	865	15555	AUAAGGGAGGUAGUAGAU	865	15573	CAUGAUCAACACUCCUAAU	2516
15573	GAUUUCGUUGGAUGAUUJ	866	15573	GAUUUCGUUGGAUGAUUJ	866	15591	AAAACUCAUCACGUAAUUC	2517
15591	UACGCCUACCUUGCGUAAAC	867	15591	UACGCCUACCUUGCGUAAAC	867	15609	GUUUACGCGAGGUAGGGGU	2518
15609	CAUUUCUCCAUAGAUUJC	868	15609	CAUUUCUCCAUAGAUUJC	868	15627	GAAUCAUCAUGGAGAAAUG	2519
15627	CUUUCUCAUGAUGGCCUUG	869	15627	CUUUCUCAUGAUGGCCUUG	869	15645	CAACGGCAUCAUCAGAAA	2520
15645	GUGUGCUUAACAGUACU	870	15645	GUGUGCUUAACAGUACU	870	15663	AGUUACUGUUUAUGACAC	2521
15663	UAUGCCGGCUCAAGGUUAG	871	15663	UAUGCCGGCUCAAGGUUAG	871	15681	CUAAACCUUJUGGCCGCAU	2522
15681	GUAGGUAGGCAUAGAACU	872	15681	GUAGGUAGGCAUAGAACU	872	15699	AGUUCUUAAGGUAGCUAC	2523
15699	UUUAGGGCAUUCUUAU	873	15699	UUUAGGGCAUUCUUAU	873	15717	AUAAAAGACUUGCCUUAAA	2524
15717	UAUCAAAAUUAUGGUUCA	874	15717	UAUCAAAAUUAUGGUUCA	874	15735	UGAACACAUUAUUGGUUA	2525
15735	AUGUCUGAGGCCAAAUGUU	875	15735	AUGUCUGAGGCCAAAUGUU	875	15753	AAACAUUJUJUGCCUCAGACAU	2526
15753	UGGACUGAGACUGACCUUA	876	15753	UGGACUGAGACUGACCUUA	876	15771	UAAGGACUGACUGACCUUA	2527

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15771	ACUAAAGGACCCUCACGAAU	877	157711	ACUAAAGGACCCUCACGAAU	877	15789	AUUCGGAGGGUCCUUJUAGU	2528
15789	UUUUGCUCACAGCAUACAA	878	15789	UUUUGCUCACAGCAUACAA	878	15807	UUJUGUAUGCUGUGAGCAAA	2529
15807	AUGCUAGUAAAACAAGGAG	879	15807	AUGCUAGUAAAACAAGGAG	879	15825	CUCUUGUUUAUCUAGCAU	2530
15825	GAUGAUUACGGGUACCGC	880	15825	GAUGAUUACGGGUACCGC	880	15843	GCAGGUACAGUAAUACU	2531
15843	CCUUAACCCAGAUCCAUCA	881	15843	CCUUAACCCAGAUCCAUCA	881	15861	UUGGUAGAUUGGGUAAAGG	2532
15861	AGAAUAAUAGGGCGAGGC	882	15861	AGAAUAAUAGGGCGAGGC	882	15879	AGCCUGCGCCUAAUAUICU	2533
15879	UGUUUUGGUCAUGAUUUG	883	15879	UGUUUUGGUCAUGAUUUG	883	15887	CAAUAUCAUCGACAAAAACA	2534
15887	GUCAAAACAGAUGGUACAC	884	15897	GUCAAAACAGAUGGUACAC	884	15915	GUGUACCAUCGUUJUGAC	2535
15915	CUUAUGAUJGAAAGGUUCG	885	15915	CUUAUGAUJGAAAGGUUCG	885	15933	CGAACCUUCAUCAUAAAG	2536
15933	GUGUCACUGGCCUAAUGAUG	886	15933	GUGUCACUGGCCUAAUGAUG	886	15951	CAUCUAUAGCCAGUGACAC	2537
15951	CCUUAACCCACUUAACAAAC	887	15951	CCUUAACCCACUUAACAAAC	887	15969	GUUJUGUAAGGGUAAAGC	2538
15969	CAUCCUAAUACAGGAGUAUG	888	15969	CAUCCUAAUACAGGAGUAUG	888	15987	CAUACUCCGUUAJGGAUG	2539
15987	GCUGGAUGGUUCUJUACUJU	889	15987	GCUGGAUGGUUCUJUACUJU	889	16005	ACAAGUGAAAAGACAUACGC	2540
16005	UAUUUUACAAUACAUJAGAA	890	16005	UAUUUUACAAUACAUJAGAA	890	16023	UUCUUAUGGUAAUUAAGAA	2541
16023	AAGUUACAUAGAUGGUUUA	891	16023	AAGUUACAUAGAUGGUUUA	891	16041	UAAGQCUCAUCAUAGUAAACU	2542
16041	ACUGGCCACAUAGUUGGACA	892	16041	ACUGGCCACAUAGUUGGACA	892	16059	UGUCCAACAUAGUGGCCAGU	2543
16059	AUGUAUUCGUAAUGGUAA	893	16059	AUGUAUUCGUAAUGGUAA	893	16077	UJAGCAUUAUCGAAUACAU	2544
16077	ACUAAUGAUAAACCUAC	894	16077	ACUAAUGAUAAACCUAC	894	16095	GUGAGGGUUAUCAUJAGU	2545
16095	CGGUACUGGGAAACCUGAGU	895	16095	CGGUACUGGGAAACCUGAGU	895	16113	ACUUCAGGUUCCAGUACCG	2546
16113	UUUUUAGGGCUAAUGUACA	896	16113	UUUUUAGGGCUAAUGUACA	896	16131	UGUACAUAGCCUCAUAAA	2547
16131	ACACCACAUACAGUUCUGC	897	16131	ACACCACAUACAGUUCUGC	897	16149	GCAAGACGUUAUGGGUGU	2548
16149	CAGGGCUAGGGGUUCUGUG	898	16149	CAGGGCUAGGGGUUCUGUG	898	16167	CACAAAGCACCUCAGGCCUG	2549
16167	GUAUUUGGUCAUUCACAGA	899	16167	GUAUUUGGUCAUUCACAGA	899	16185	UICUJUGUAUJGACAAUAC	2550
16185	ACUUCACUUCGUUCGGGUG	900	16185	ACUUCACUUCGUUCGGGUG	900	16203	CACCGCAACGGAUGUGAAGU	2551
16203	GCCUGUAUJAGGAGACAU	901	16203	GCCUGUAUJAGGAGACAU	901	16221	AUGGUCUCCUAUACAGGC	2552
16221	UCCCCAUUGGUUCAGUGCU	902	16221	UCCCCAUUGGUUCAGUGCU	902	16239	AGCACUUCGCAACAUAGGA	2553
16239	UGCUUAUGACCAUJGUUU	903	16239	UGCUUAUGACCAUJGUUU	903	16257	AAAUIGCAUCJGGUCAUAGCA	2554
16257	UCAACAUACACAAAUJAG	904	16257	UCAACAUACACAAAUJAG	904	16275	CJAAUJUJUGGUAGUGUIGA	2555
16275	GUGUUGUGGUAAAUCCU	905	16275	GUGUUGUGGUAAAUCCU	905	16293	AGGGAUUACAGACAACAC	2556
16293	UAGUUGGUCAUGGCCAG	906	16293	UAGUUGGUCAUGGCCAG	906	16311	CGGGGGCAUUGGUACAAUJA	2557
16311	GGUUGUCAUGGUCAUGGU	907	16311	GGUUGUCAUGGUCAUGGU	907	16329	CAUCAGUAGACAUACACACC	2558
16329	GUGACACAAUCGUACUJAG	908	16329	GUGACACAAUCGUACUJAG	908	16347	CJAGAUJACAGUUGGUUCAC	2559
16347	GGAGGUAGGAGCUAAUAU	909	16347	GGAGGUAGGAGCUAAUAU	909	16365	AAUAUAUAGGUCAUCUCC	2560
16365	UCCAAGGUACACAUAGCUC	910	16365	UCCAAGGUACACAUAGCUC	910	16383	GAGGCCUUAGGUACUJUGCA	2561
16383	CCCCAUUGGUUCAUUAU	911	16383	CCCCAUUGGUUCAUUAU	911	16401	AUAAUGGAAAACUAAUGGG	2562
16401	UGUGCUAAJGGGUAGGUU	912	16401	UGUGCUAAJGGGUAGGUU	912	16419	AAACCUUGCCAUJUAGCA	2563
16419	UUUGGUUUAUACAAAAACA	913	16419	UUUGGUUUAUACAAAAACA	913	16437	UGUJJUUJGUUAACACAA	2564
16437	ACAUUGGUAGGGAGUGACA	914	16437	ACAUUGGUAGGGAGUGACA	914	16455	UGUCACUGCCUACACAU	2565
16455	AUGGUACACUACGUUCAUG	915	16455	AUGGUACACUACGUUCAUG	915	16473	CAUJGAAGGUAGGUACAU	2566
16473	GCGAUUAGGCAACAUJGUU	916	16473	GCGAUUAGGCAACAUJGUU	916	16491	AAUCACAUAGGUAGGUAC	2567
16491	UGGACUAAUAGGUCCGAU	917	16491	UGGACUAAUAGGUCCGAU	917	16509	AAUCACAUAGGUAGGUAC	2568
16509	UACAUACUUGGCCAACACUU	918	16509	UACAUACUUGGCCAACACUU	918	16527	AAGUGUJGGCAAGUAGUA	2569

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16527	UGUACUGAGAGACUCAAGC	919	16527	UGUACUGAGAGACUCAAGC	919	16545	GCLUGAGUCUCUCAGUACA	2570
16545	CUUUUCGCGAGCGAAACGC	920	16545	CUUUUCGCGAGCGAAACGC	920	16563	GCGGUUUUCUGCGCGAAAG	2571
16563	CUCAAAGCCACUGAGAAA	921	16563	CUCAAAGCCACUGAGAAA	921	16581	UUUCUGGUUGGGGUUGAG	2572
16581	ACAUUUAGCUGUCAUAUG	922	16581	ACAUUUAGCUGUCAUAUG	922	16599	CAUAGACAGCUUAAAAG	2573
16599	GGUAUUGGCCACUGUACGCG	923	16599	GGUAUUGGCCACUGUACGCG	923	16617	CGCGUACAGUGGCAAUC	2574
16617	GAAGGUACUCUCUCAAGAG	924	16617	GAAGGUACUCUCUCAAGAG	924	16635	CUCUGUICAGAGAGUACUUC	2575
16635	GAUUUGGCAUCUUCUCAUGGG	925	16635	GAUUUGGCAUCUUCUCAUGGG	925	16653	CCOUGAAAAGAUGCAAUUC	2576
16653	GAGGUUGGAAAAACCUAGAC	926	16653	GAGGUUGGAAAAACCUAGAC	926	16671	GUUAGGUUUUCCUACCUC	2577
16671	CCACCAUUGAACAGAACU	927	16671	CCACCAUUGAACAGAACU	927	16689	AGUUUCUGUUCUAGGGUG	2578
16689	UAUGUCUUACUGGUUACCC	928	16689	UAUGUCUUACUGGUUACCC	928	16707	GGUAAACCAGUAAAAGACAU	2579
16707	CGUGUACUAAAAGUAGUA	929	16707	CGUGUACUAAAAGUAGUA	929	16725	UACUAAUAAAUGGUACACG	2580
16725	AAAGGUACAGAUUUGGAGAG	930	16725	AAAGGUACAGAUUUGGAGAG	930	16743	ACUCUCCAUUGGUACUUU	2581
16743	UACACCUUUGAAAAAGGUG	931	16743	UACACCUUUGAAAAAGGUG	931	16761	CACCUUUCUAAAGGGUGUA	2582
16761	GACUAGGGUGAUGCUGUUG	932	16761	GACUAGGGUGAUGCUGUUG	932	16779	CAACAGCAUCCACCAUAGUG	2583
16779	GUGUACAGAGGUACUACGA	933	16779	GUGUACAGAGGUACUACGA	933	16797	UCGUAGUACCUUGGUACAC	2584
16797	ACAUUACAAGUUGAAUGUUG	934	16797	ACAUUACAAGUUGAAUGUUG	934	16815	CAACAUUACUACUUGUAUGU	2585
16815	GGGAAUUCUUCUGGUUGA	935	16815	GGGAAUUCUUCUGGUUGA	935	16833	UCAACACAAAGUAAUCACC	2586
16833	ACAUUCUACACUGUAAUGC	936	16833	ACAUUCUACACUGUAAUGC	936	16851	GCAUUAACAGUGUGGAGAU	2587
16851	CCACCUUAGUGGCCACUUC	937	16851	CCACCUUAGUGGCCACUUC	937	16869	GAGUAGGUUGGACUAAAGUG	2588
16869	CUAGUGGCCACAGGACAC	938	16869	CUAGUGGCCACAGGACAC	938	16887	AGGUCCUUGGGACUAG	2589
16887	UAUGUGGAGAAUACUGGCU	939	16887	UAUGUGGAGAAUACUGGCU	939	16905	AGCCAGUAAUUCACUACAU	2590
16905	UJGUACCCAACACUACACA	940	16905	UJGUACCCAACACUACACA	940	16923	UGUAGAGUUGGGGUACAA	2591
16923	AUCUCAGAUUGGUUUCUA	941	16923	AUCUCAGAUUGGUUUCUA	941	16941	UAGAAAACUCUACUGAGAU	2592
16941	AGCAAAUGGUUACAAUUC	942	16941	AGCAAAUGGUUACAAUUC	942	16959	GAUAAAUGCAACAUUGCU	2593
16959	CAAAAGGUUGGGCAUGGAAA	943	16959	CAAAAGGUUGGGCAUGGAAA	943	16977	UUUCAUGGCCACUUUUG	2594
16977	AAGGUACUCUACACUCCAA	944	16977	AAGGUACUCUACACUCCAA	944	16995	CUUJGGAGUGUAGGUACU	2595
16995	GGACCCACCUUGGUACUGUA	945	16995	GGACCCACCUUGGUACUGUA	945	17013	UACCAUGUACCCAGGUUC	2596
17013	AGAGGUACAUUUUGGCCAUCG	946	17013	AGAGGUACAUUUUGGCCAUCG	946	17031	CGAUJGGCAAAAGACU	2597
17031	GGACUUCUGCUUCUAAUACC	947	17031	GGACUUCUGCUUCUAAUACC	947	17049	GGUUAUAGGGCAAGGUCC	2598
17049	CCACUCUGCUUCUAAUAGUGU	948	17049	CCACUCUGCUUCUAAUAGUGU	948	17067	ACACUACUGGCCAGCAUGG	2599
17067	UUAUACGGCAUCUGCUUCUAG	949	17067	UUAUACGGCAUCUGCUUCUAG	949	17085	CAJGAGAGGAUCGCCGUUA	2600
17085	GCAGCGUGUGUAGGCCUAU	950	17085	GCAGCGUGUGUAGGCCUAU	950	17103	AUAGGGCAUCAACAGCUC	2601
17103	UGUGAAAAAGGCCAUAAA	951	17103	UGUGAAAAAGGCCAUAAA	951	17121	AUJJUUAUGCCUUUUCACA	2602
17121	UAUUUUGGCCAUAAA	952	17121	UAUUUUGGCCAUAAA	952	17139	AUJUUAUCUAGGGAAAUA	2603
17139	UGAGGUAGAAUCAUCACUG	953	17139	UGAGGUAGAAUCAUCACUG	953	17157	CAGGUAGAUUCUACUACAA	2604
17157	GCGCGUGGCCGCGGUAGGU	954	17157	GCGCGUGGCCGCGGUAGGU	954	17175	ACUJCUACGGCGCACGGC	2605
17175	UGUUUUAGGUAAAUCUAAAG	955	17175	UGUUUUAGGUAAAUCUAAAG	955	17193	CUUJGAAUAAAUCAAAACA	2606
17193	GUGAAUUCACACUAGAAC	956	17193	GUGAAUUCACACUAGAAC	956	17211	GUUCUAGGUUGGAAUUCAC	2607
17211	CAGUAUGUUUCUGCAUC	957	17211	CAGUAUGUUUCUGCAUC	957	17229	CAGUGGAGAAAACAUACUG	2608
17229	GUAAAUGCAUCUGCCAGAAA	958	17229	GUAAAUGCAUCUGCCAGAAA	958	17247	UJUJUGGCAAUUCUAC	2609
17247	ACAAACUGCGACAUUUGUAG	959	17247	ACAAACUGCGACAUUUGUAG	959	17265	CUACAAUGGUAGCGAGUUGU	2610
17265	GUCCUUUGAUAGAAAUCUCUA	960	17265	GUCCUUUGAUAGAAAUCUCUA	960	17283	UAGAGAUUUCUCAAAAGAC	2611

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17283	AUGGCUACUAAUUAUGACU	961	17283	AUGGCUACUAAUUAUGACU	961	17301	AGUCAUAAUUAUGUAGCCAU	2612
17301	UUGAGUGGUUGCUCAUUGCUA	962	17301	UUGAGUGGUUGCUCAUUGCUA	962	17319	UAGGCUUUGACAACACUCAA	2613
17319	AGACUUCGGCAAAACACU	963	17319	AGACUUCGGCAAAACACU	963	17337	AGUGCUUUGACAAGUGCUJ	2614
17337	UACCGUCUAAUUGGCCAUC	964	17337	UACCGUCUAAUUGGCCAUC	964	17355	GAUCGCCAAUUAUGCCAU	2615
17355	CCUGCUCAAUUACCAGCCC	965	17356	CCUGCUCAAUUACCAGCCC	965	17373	GGCUGGUAAUJAGGCAGG	2616
17373	CCCCGCAACAUUCCUGACUA	966	17373	CCCCGCAACAUUCCUGACUA	966	17391	UAGUCAGCAAUUGGCCGGG	2617
17391	AAAGGCACACUAGAACAG	967	17391	AAAGGCACACUAGAACAG	967	17409	CUGGUUCUAGUGGCCUUU	2618
17409	GAUAAUUIUAAUUCAGUGU	968	17409	GAUAAUUIUAAUUCAGUGU	968	17427	ACACUGAAUAAAUAUUC	2619
17427	UGCAGACUUAUGAAAACAA	969	17427	UGCAGACUUAUGAAAACAA	969	17445	UJGUUUUCAUAAUGUCUGCA	2620
17445	AUAGGUCCAGACAUGUCC	970	17445	AUAGGUCCAGACAUGUCC	970	17463	GGAAACAUGUCUGGUACCUAU	2621
17463	CUUGGAACUUGCCGUU	971	17463	CUUGGAACUUGCCGUU	971	17481	ACCGGGCAGACAUUCCAG	2622
17481	UGUCCUGCGUAAUUGUUG	972	17481	UGUCCUGCGUAAUUGUUG	972	17499	CAACAAUUCAGCCAGGACA	2623
17499	GACACUGUGAGUGGUUAG	973	17499	GACACUGUGAGUGGUUAG	973	17517	CUAAAGCACUJCAGAGUGUC	2624
17517	GUUUAUGACAAUAAUGCUA	974	17517	GUUUAUGACAAUAAUGCUA	974	17535	UJAGCUUUAUUGCUAAUAAAC	2625
17535	AAAGCACACAGGAAUAGU	975	17535	AAAGCACACAGGAAUAGU	975	17553	ACUUAUCCUUGUGGUUUU	2626
17553	UCAGCUCAUAGCUUCAAA	976	17553	UCAGCUCAUAGCUUCAAA	976	17571	UUUJUGAAGCAUAGGCUGA	2627
17571	AUGUUCUCAAAAGGUUUA	977	17571	AUGUUCUCAAAAGGUUUA	977	17589	UJACACCUUJUGUAAACAU	2628
17589	AUUACACALIGAUJUUCAU	978	17589	AUUACACAUAGAUJUUCAU	978	17607	AUGAAAACAUCAUAGUGUAAU	2629
17607	UCUGGCAAUCAACAGACUC	979	17607	UCUGGCAAUCAACAGACUC	979	17625	GAGGUCUGUUGAUJUGCAGA	2630
17625	CAAAUAGGGGUUAGAG	980	17625	CAAAUAGGGGUUAGAG	980	17643	CUCUJUACAACGCCUAAUUG	2631
17643	GAUAAUUCUJAACGCAUC	981	17643	GAUAAUUCUJAACGCAUC	981	17661	GAUJGCUGUUAAGAAAUC	2632
17661	CGUGCUUJGGAGAAAAGCUC	982	17661	CGUGCUUJGGAGAAAAGCUC	982	17679	CAGGUUUUCUJGCAAGGAGG	2633
17679	GUUUUAUUCUACCUUUA	983	17679	GUUUUAUUCUACCUUUA	983	17697	UAUJAGGUGAGAUAAAAC	2634
17697	AUUCACAGAACGGCUJAG	984	17697	AUUCACAGAACGGCUJAG	984	17715	CUACAGCGUUCUGUGAAUJ	2635
17715	GUUCAAAAACUUCUAGGAU	985	17715	GUUCAAAAACUUCUAGGAU	985	17733	AUCCUAAGUUUUUGAAGC	2636
17733	UUGCCUACGGCAGCUGU	986	17733	UUGCCUACGGCAGCUGU	986	17751	CAACAGCUGUGGUAGGCCAA	2637
17751	GAUUCAUACAGGGGUUCUG	987	17751	GAUUCAUACAGGGGUUCUG	987	17769	CAGAAACCCUGUGAUGAAC	2638
17769	GAUAAUGCUAUGCUJAU	988	17769	GAUAAUGCUAUGCUJAU	988	17787	AUAGCAGAUUCAUAAUUC	2639
17787	UUCACACAAACUACUJAAA	989	17787	UUCACACAAACUACUJAAA	989	17805	UJUCGUAGUUGUGGUAGAA	2640
17805	ACAGCACACUJUUCGUAAUG	990	17805	ACAGCACACUJUUCGUAAUG	990	17823	CAUJUACAAGAGUGUGCUJ	2641
17823	GUCAACCGCJUUCAUJUGG	991	17823	GUCAACCGCJUUCAUJUGG	991	17841	CCACAUJGAAGGGGUUGAC	2642
17841	GUUAUCACAGGGCAAAA	992	17841	GUUAUCACAGGGCAAAA	992	17859	UUUUJGCCUUGUGAUJGU	2643
17859	AUUGGCAUJJUGUGCUAA	993	17859	AUUGGCAUJJUGUGCUAA	993	17877	UJAGCACAACAUUGCCAU	2644
17877	AUGUCUGAUJAGGAUCUU	994	17877	AUGUCUGAUJAGGAUCUU	994	17895	AAAGAUJCUCUACAGACAU	2645
17895	UAUGACAAAACUGCAAUUA	995	17895	UAUGACAAAACUGCAAUUA	995	17913	UAAAUJGGCAGUUGCUAU	2646
17913	ACAAGUCUAGAAAACCAC	996	17913	ACAAGUCUAGAAAACCAC	996	17931	GUGGUUUUCUJAGACIJGU	2647
17931	CGUCGCAUJUGGGCUACAU	997	17931	CGUCGCAUJUGGGCUACAU	997	17949	AUGUAGCCACAUUGCGAGG	2648
17949	UUACAAGGCAAAAUGUAA	998	17949	UUACAAGGCAAAAUGUAA	998	17967	UJACAUUUUCUGGUUGUAA	2649
17967	ACUGGACUJUJJUJUAGGACU	999	17967	ACUGGACUJUJJUAGGACU	999	17985	AGUCCUUAAAAGUCCAGU	2650
17985	UGUAGUAAGAUCAUJUACUG	1000	17985	UGUAGUAAGAUCAUJUACUG	1000	18003	CAGUAAUJGAUCUJUACUCA	2651
18003	GGCUUCAUCCUACACAGG	1001	18003	GGCUUCAUCCUACACAGG	1001	18021	CCUGUGUAGGUGAAGACCC	2652
18021	GCACCUACACCUACAGCG	1002	18021	GCACCUACACCUACAGCG	1002	18039	CGCUGAGGUGUGUAGGUGC	2653

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18039	GUUGAUAAAAGUUCAGA	1003	18039	GUUGAUAAAAGUUCAGA	1003	18057	UCUUGAACUUAAAUAUCAAC	2654
18057	ACUGAAGGAUUAUGGUUG	1004	18057	ACUGAAGGAUUAUGGUUG	1004	18075	CAACACAUAAAUCUUUCAGU	2655
18075	GACAUACCAGGCAUACCAA	1005	18075	GACAUACCAGGCAUACCAA	1005	18093	UUGGGUAGCCUCGUAGGUUCU	2656
18093	AAGGACAUGACCUACGUA	1006	18093	AAGGACAUGACCUACGUA	1006	18111	UACGGUAGGGUAGGUUCU	2657
18111	AGACUCAUCUCAUGAUGG	1007	18111	AGACUCAUCUCAUGAUGG	1007	18129	CCAUCAUAGAGAUGAGUCU	2658
18129	GGUUUCAAAUGAAUUACC	1008	18129	GGUUUCAAAUGAAUUACC	1008	18147	GGUAAUUCAUUUUAAACC	2659
18147	CAAGUCAAUGGUUACCUA	1009	18147	CAAGUCAAUGGUUACCUA	1009	18165	UAGGGUAAACAUUAGCUUG	2660
18165	AAUAUGUUUAUCACCGCG	1010	18165	AAUAUGUUUAUCACCGCG	1010	18183	CGGGGUGGUAAAACAUUJ	2661
18183	GAAGAAGCJAUUCGUCACG	1011	18183	GAAGAAGCJAUUCGUCACG	1011	18201	CGUGACGAAUAGCUUCUJC	2662
18201	GUUCGUGCGUGGGAUUGGCCU	1012	18201	GUUCGUGCGUGGGAUUGGCCU	1012	18219	AGCCTAAUCCACGCACGAAAC	2663
18219	UUJGAUGUAAGGGCJUGUC	1013	18219	UUJGAUGUAAGGGCJUGUC	1013	18237	GACAGCCCUCUCAUCUAAA	2664
18237	CAUGCAACUAGAAGUGCUG	1014	18237	CAUGCAACUAGAAGUGCUG	1014	18255	CAGCAUCUAGUUGGUCAUG	2665
18255	GUUGGUACUAACCUACUC	1015	18255	GUUGGUACUAACCUACUC	1015	18273	GAGGGUAGGUAGGUACCCAC	2666
18273	CUCCAGCUAGGAUUCUA	1016	18273	CUCCAGCUAGGAUUCUA	1016	18291	UAGAAAAUCCUAGCUGGAG	2667
18291	ACAGGGUUAACUUAUGAG	1017	18291	ACAGGGUUAACUUAUGAG	1017	18309	CUACUAAGUUAACCCUGU	2668
18309	GCUGUACCGACUGGUUAUG	1018	18309	GCUGUACCGACUGGUUAUG	1018	18327	CAUAAACGUUGGUACAGC	2669
18327	GUUGGACACUGAAAAAAACA	1019	18327	GUUGGACACUGAAAAAAACA	1019	18345	UGUUAUJJUUCAGUGUCAAC	2670
18345	ACAGAAUUCACCAAGUUA	1020	18345	ACAGAAUUCACCAAGUUA	1020	18363	UAAUCUCUGGGUAGAUUCIGU	2671
18363	AAUGCAAAACCCACCAAG	1021	18363	AAUGCAAAACCCACCAAG	1021	18381	CUGGGGAGGUUUUJGCAU	2672
18381	GGUGGACCAAGUAAAACAU	1022	18381	GGUGGACCAAGUAAAACAU	1022	18399	GAUGUUAAACUGGUACCC	2673
18399	CUUAAUACCACUCAUGUA	1023	18399	CUUAAUACCACUCAUGUA	1023	18417	UAUCAUGAGGUAGUAUAG	2674
18417	AAAGGCUUJGCCUGGAUG	1024	18417	AAAGGCUUJGCCUGGAUG	1024	18435	CAUUCUAGGGGGAAAGCCUUU	2675
18435	GUAGUGCGUAAAAGUAG	1025	18435	GUAGUGCGUAAAAGUAG	1025	18453	CUAUCUAAAACGACCUAC	2676
18453	GUACAAAUGSCUCAGGUA	1026	18453	GUACAAAUGSCUCAGGUA	1026	18471	UAUCACUGAGCAUUGUAC	2677
18471	ACACUGAAAAGGGAUUGUCAG	1027	18471	ACACUGAAAAGGGAUUGUCAG	1027	18489	CUGACAAUCCUUCAGUGU	2678
18489	GCACAGAGUGGUUGGUUC	1028	18489	GCACAGAGUGGUUGGUUC	1028	18507	GGACGAACACGACUCUGUC	2679
18507	CUUUGGGCGCAUGGCUUJG	1029	18507	CUUUGGGCGCAUGGCUUJG	1029	18525	CAAAGCCAUUGGCCAAAG	2680
18525	GAGCUCUACAUCAAGAUG	1030	18525	GAGCUCUACAUCAAGAUG	1030	18543	ACUUCUUGAUAGUAAGCCUC	2681
18543	UACUUUUGCUAAAGGUUGAC	1031	18543	UACUUUUGCUAAAGGUUGAC	1031	18561	GUCAACUUCUAGAAAGUA	2682
18561	CGUGAAAAGAACGUUGUUC	1032	18561	CGUGAAAAGAACGUUGUUC	1032	18579	GACAAACGUUCUUCUUCAGG	2683
18579	CGUGUGACAAAACGUGCAA	1033	18579	CGUGUGACAAAACGUGCAA	1033	18597	UJGACGUUGGUUCACACAG	2684
18597	ACUUGCUUJCUACUCAU	1034	18597	ACUUGCUUJCUACUCAU	1034	18615	AUGAAUGUAGAAAAGCAAGU	2685
18615	UCAGAUACUJUAGGCCGU	1035	18615	UCAGAUACUJUAGGCCGU	1035	18633	AGCAGGCAUAGUAUCUGA	2686
18633	UGGAAUCAUJUCUGGGGU	1036	18633	UGGAAUCAUJUCUGGGGU	1036	18651	AACCCACAGAAAGAUUCCA	2687
18651	UUUGACUAAUGGUCAUAA	1037	18651	UUUGACUAAUGGUCAUAA	1037	18669	GGUUAUAGACAUAGUCAA	2688
18669	CAUUUAUGAUUGAUUC	1038	18669	CAUUUAUGAUUGAUUC	1038	18687	GAACAUCAUCAUAAAUGG	2689
18687	CAGCAGUGGGCUUACGG	1039	18687	CAGCAGUGGGCUUACGG	1039	18705	CCGUAAAAGCCCCACUGGU	2690
18705	GUUAACCUJUCAGGUAC	1040	18705	GUUAACCUJUCAGGUAC	1040	18723	GGUACUCUCAUGGUUCAC	2691
18723	CAUGACCAACAUJUGCCAG	1041	18723	CAUGACCAACAUJUGCCAG	1041	18741	CCUGGCAAUUGGUUCAG	2692
18741	GUACAUGAAAUGCAUG	1042	18741	GUACAUGAAAUGCAUG	1042	18759	CAUGUGCAUAAAUGGUAC	2693
18759	GUGGCUAGGUUGGUAGCUA	1043	18759	GUGGCUAGGUUGGUAGCUA	1043	18777	UAGCAUCACAUAGCCAC	2694
18777	AUCAUGACUAGGUUUAG	1044	18777	AUCAUGACUAGGUUUAG	1044	18795	CUAAACAUCAUGGUAGAU	2695

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18795	GCAGGUCCAUGAGGUUUG	1045	18795	GCAGGUCCAUGAGGUUUG	1045	18813	CAAAGCACUCUCAUGGACUGC	2696
18813	GUUAAGCGGGUUGAUUGGU	1046	18813	GUUAAGCGGGUUGAUUGGU	1046	18831	ACCAAAUCAACGGCUUAAC	2697
18831	UCUGUUJUGAUAUCCCCUAUA	1047	18831	UCUGUUJUGAUAUCCCCUAUA	1047	18849	UAUJAGGGGUUAUCAACAGA	2698
18849	UAUAGGAJUGAACUGAGGG	1048	18849	UAUAGGAJUGAACUGAGGG	1048	18867	CCCUUCAGGUUCAUCUCCUAU	2699
18867	GUAAAUCUJUGCUUGCGAA	1049	18867	GUAAAUCUJUGCUUGCGAA	1049	18885	UUCGUAGGAGGAAUUAAC	2700
18885	AAGGUACAAACAUGGUUG	1050	18885	AAGGUACAAACAUGGUUG	1050	18903	CAACCAAGGUUGGUACUUCAC	2701
18903	GUGAAAGUCCUGCAUJGUUG	1051	18903	GUGAAAGUCCUGCAUJGUUG	1051	18921	CAACCAAGGUUGGUACUUCAC	2702
18921	GCGUAGAUJAGGUUICCAGUUC	1052	18921	GCGUAGAUJAGGUUICCAGUUC	1052	18939	GAACUGGAAAACUUAUAGC	2703
18939	CUCUAGGACAUJGGAAUAC	1053	18939	CUCUAGGACAUJGGAAUAC	1053	18957	GAUJUCCAAGUCAUGAAG	2704
18957	CAAAAGGCCUAUCAAGUGUG	1054	18957	CAAAAGGCCUAUCAAGUGUG	1054	18975	CACACUJGUAGGCCUUGG	2705
18975	GUGGCCUCAGGCUGAAGUAG	1055	18975	GUGGCCUCAGGCUGAAGUAG	1055	18993	CUACUUCAGGCCUGAGGCAC	2706
18993	GAAUGGGAAQGUUCUACGAUG	1056	18993	GAAUGGGAAQGUUCUACGAUG	1056	19011	CAUJGUAGAAUCUCCAUUC	2707
19011	GCUCAGGCCAUJGUAGGACA	1057	19011	GCUCAGGCCAUJGUAGGACA	1057	19029	UGUCACUCUACAUJGGUGAGC	2708
19029	AAAGCUUACAAAAAUAGG	1058	19029	AAAGCUUACAAAAAUAGG	1058	19047	CCUCUJGUAGGUUAGGUU	2709
19047	GAACUCUJGUUACUUAUG	1059	19047	GAACUCUJGUUACUUAUG	1059	19065	CAUJAGAAUJGUAGGUUC	2710
19065	GUACACACALICAGGUAAA	1060	19065	GUACACACUACAGGUAAA	1060	19083	AUJUJAUCUGGUAGGUUGAGC	2711
19083	UUCACUGAUJGGGUUGUU	1061	19083	UUCACUGAUJGGGUUGUU	1061	19101	AACAAACACCAJGUUGAA	2712
19101	UGGUUUJGGAAUUGUACG	1062	19101	UGGUUUJGGAAUUGUACG	1062	19119	CGUJUACAUUCCAAAACAA	2713
19119	GUUGAUJGUACCAGCA	1063	19119	GUUGAUJGUACCAGCA	1063	19137	UGGUGGUAAAGAUCAAC	2714
19137	AUGGCAAAUJGUUGUAGGU	1064	19137	AUGGCAAAUJGUUGUAGGU	1064	19155	ACCUACACACAAUJGUAAU	2715
19155	UUUGACACAAAGAGCUUGU	1065	19155	UUUGACACAAAGAGCUUGU	1065	19173	ACAAAGACUUCUJGUUGUAAA	2716
19173	UCAAAUCUUGACUUCACAG	1066	19173	UCAAAUCUUGACUUCACAG	1066	19191	GUUGGUAGGUUAGGUUGAA	2717
19191	GCUGUGAUJGGGUUGGU	1067	19191	GCUGUGAUJGGGUUGGU	1067	19209	AACUACCCAUCAAGGG	2718
19209	UGUGAUJGUAGGUAGGU	1068	19209	UGUGAUJGUAGGUAGGU	1068	19227	CAUJGUAGGUUACAUACAA	2719
19227	GCAUUCCCACACUCCAGCU	1069	19227	GCAUUCCCACACUCCAGCU	1069	19245	AAGCUGGGAGGUUGGAAUGC	2720
19245	UCCGAUAAAAGGUCAUUA	1070	19245	UCCGAUAAAAGGUCAUUA	1070	19263	UAAAUGCAUJGUUUAUCGAA	2721
19263	ACUAAAUAAGCAAUUGC	1071	19263	ACUAAAUAAGCAAUUGC	1071	19281	GCAUJGUUAAAUAUAGU	2722
19281	CCUUUCUJUJUACUUAUCUG	1072	19281	CCUUUCUJUJUACUUAUCUG	1072	19299	CAGAAUJGUAAAAGAAAGG	2723
19299	GAUAGGUCCJUGAGGUUC	1073	19299	GAUAGGUCCJUGAGGUUC	1073	19317	GAGGACUACAGGACUAC	2724
19317	CAUGGCAAAACAAGUAGGU	1074	19317	CAUGGCAAAACAAGUAGGU	1074	19335	ACACUACUJGUUJGCAUG	2725
19335	UGGGAUJGUAGGUUC	1075	19335	UGGGAUJGUAGGUUC	1075	19353	GAACAUJGUCAUUAUCCGA	2726
19353	CACUCAAAUCUGCUACGU	1076	19353	CACUCAAAUCUGCUACGU	1076	19371	CAUJGUAGGUAGGUUGG	2727
19371	GUAUUACACGUAGCAUU	1077	19371	GUAUUACACGUAGCAUU	1077	19389	AAUJGUACUJGUUUAUAGC	2728
19389	UAGGGUGGUJGUUGGUUGCA	1078	19389	UAGGGUGGUJGUUGGUUGCA	1078	19407	UGCAAAACAGGCCACCUAA	2729
19407	AGACACCAUGCAAAAGAGU	1079	19407	AGACACCAUGCAAAAGAGU	1079	19425	ACUJGUJGUUGGUUCU	2730
19425	UACCGACAGUACUJGUUGAUG	1080	19425	UACCGACAGUACUJGUUGAUG	1080	19443	CAUCCAGGUACUGUGGUA	2731
19443	GCAUAAAUAUJGUAGGUUU	1081	19443	GCAUAAAUAUJGUAGGUUU	1081	19461	AAAUCAUCAUJGUAGGU	2732
19461	UCUGCUGGUJGUUGGUUCU	1082	19461	UCUGCUGGUJGUUGGUUCU	1082	19479	AUAGGGCUAAUCCAGCAGA	2733
19479	UGGAUJGUACAAACAUJGU	1083	19479	UGGAUJGUACAAACAUJGU	1083	19497	CAAAUUGUUJGUAAAUCCA	2734
19497	GAUACUUAUAAACCUGGGA	1084	19497	GAUACUUAUAAACCUGGGA	1084	19515	UCCACAGGUUUAAGGUAC	2735
19515	AUACAUUUUACCGGUUAC	1085	19515	AUACAUUUUACCGGUUAC	1085	19533	GUACCUUGGUAAAGGUAUU	2736
19533	CAGGUUJGUAGAAAUGGG	1086	19533	CAGGUUJGUAGAAAUGGG	1086	19551	CCACAUUUUUCUAAACUCUG	2737

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19551	GCUUUAAAUGUUUAUA	1087	19551	GUUAAAUGUUUAUA	1087	19569	UAUUAACAAUUAAGC	2738
19569	AAAGGACACUUUAGGAC	1088	19569	AAAGGACACUUUAGGAC	1088	19587	GUCAUCUAAAUGUCCUJJ	2739
19587	CACGCCGGGAAGCACUG	1089	19587	CACGCCGGGAAGCACUG	1089	19605	CAGGUGCUUCCGGCGUG	2740
19605	GUUUCCAUCUUAAAUAUG	1090	19605	GUUUCCAUCUUAAAUAUG	1090	19623	CAUUAUAAAUGAUGGAAAC	2741
19623	GCUGUUUACACAUAAAUAUG	1091	19623	GCUGUUUACACAUAAAUAUG	1091	19641	CUACCUUCAUAAAUGGAAAC	2742
19641	GAUGGUUAUUGAUGGGAGA	1092	19641	GAUGGUUAUUGAUGGGAGA	1092	19659	UCUCCACAAUAAAUCACU	2743
19659	AUCUUUJGAAAUAAGCAA	1093	19659	AUCUUUJGAAAUAAGCAA	1093	19677	UUGUCIUUAAAUCAAAGAU	2744
19677	ACACUUCUCCGUUAAAUGU	1094	19677	ACACUUCUCCGUUAAAUGU	1094	19695	CAACAUUAAAAGGAAGUGU	2745
19695	GCAUJUJGCUUUGGCCUA	1095	19695	GCAUJUJGCUUUGGCCUA	1095	19713	UAGCCCCAAAGCUAAUGC	2746
19713	AAGCGUAAACAUUAAAACAG	1096	19713	AAGCGUAAACAUUAAAACAG	1096	19731	CUGGUUAAAUGUACGGCU	2747
19731	GUGCCAGAGAUUAAAUAUC	1097	19731	GUGCCAGAGAUUAAAUAUC	1097	19749	GUACUUCUAAAUCUGGCCAC	2748
19749	CUCAAAUAUJUUGGGUGU	1098	19749	CUCAAAUAUUGGGUGU	1098	19767	CAACACCCAAAUAUUGAG	2749
19767	GAUAUUCGGCUUACUACUG	1099	19767	GAUAUUCGGCUUACUACUG	1099	19785	CAGGUUAAAUGCAGC	2750
19785	GUAAUCUGGGACUACAAAA	1100	19785	GUAAUCUGGGACUACAAAA	1100	19803	UJJGUAGUOCAGAUUAC	2751
19803	AGAGAAGGCCAGCACAU	1101	19803	AGAGAAGGCCAGCACAU	1101	19821	CAUGUGCUUCCGGCUUUCU	2752
19821	GUACUACAAUAGGUGUCU	1102	19821	GUACUACAAUAGGUGUCU	1102	19839	AGACACCUCUJGUAGAUAC	2753
19839	UGCACAAUAGCAGACAUU	1103	19839	UGCACAAUAGCAGACAUU	1103	19857	CAAUGCAGUCUAGUGGCA	2754
19857	GCCAAGAAACCUACUGAGA	1104	19857	GCCAAGAAACCUACUGAGA	1104	19875	UCUCAUGGUUUCUGGCC	2755
19875	AGUGCUUJGUUCUUCUACUUA	1105	19875	AGUGCUUJGUUCUUCUACUUA	1105	19893	UAAAUGGAAACAAGCACU	2756
19893	ACUGUCUJGUUUGAUUGGU	1106	19893	ACUGUCUJGUUUGAUUGGU	1106	19911	UACCAUCUAAAAGACAGU	2757
19911	AGAGUGGAAGGACAGGUAG	1107	19911	AGAGUGGAAGGACAGGUAG	1107	19929	CUACCUUCGUUCCACUCU	2758
19929	GAUUCUJGUAGAACGCC	1108	19929	GAUUCUJGUAGAACGCC	1108	19947	GGGGUUCUAAAAGGU	2759
19947	CGUAAUJGUUJGUUAAAUA	1109	19947	CGUAAUJGUUJGUUAAAUA	1109	19965	UAAAUCACUACUUCUACU	2760
19965	ACAGAAGGUUCAGUCAAG	1110	19965	ACAGAAGGUUCAGUCAAG	1110	19983	CUUJGUAGGUUACUUCU	2761
19983	GUUCUAAACCUUCAAAAGG	1111	19983	GUUCUAAACCUUCAAAAGG	1111	20001	CCUJGUAGGUUAGACCC	2762
20001	GGACCAAGCACAAGCUAGCG	1112	20001	GGACCAAGCACAAGCUAGCG	1112	20019	CGCUJGUUGGUCCGGUC	2763
20019	GUCAAUGGAGUCACAUUA	1113	20019	GUCAAUGGAGUCACAUUA	1113	20037	UAAAUGGACUCAUUGAC	2764
20037	AUUGGAGAAUJGUUAAAUA	1114	20037	AUUGGAGAAUJGUUAAAUA	1114	20055	UUUUUACUGAUUCUCCAAU	2765
20055	ACACAGUUAACUACUUA	1115	20055	ACACAGUUAACUACUUA	1115	20073	UAAAUGGUAGUAAACUGUGU	2766
20073	AAGAAAUGGUAGACGGCAUUA	1116	20073	AAGAAAUGGUAGACGGCAUUA	1116	20091	UAAAUGCCGUUACUUUCU	2767
20091	AUUCAACAGUUGGCCGAAA	1117	20091	AUUCAACAGUUGGCCGAAA	1117	20109	UUUAGGCAACUGUUGAAU	2768
20109	ACCUACUUAUCUACAGCA	1118	20109	ACCUACUUAUCUACAGCA	1118	20127	UGCUUCUGGUAAAUGGU	2769
20127	AGAGACUUAUGGAGGUUA	1119	20127	AGAGACUUAUGGAGGUUA	1119	20145	UAAAUCUCUAAUGUCUCU	2770
20145	AAGCCCAGAUCACAAUUG	1120	20145	AAGCCCAGAUCACAAUUG	1120	20163	CCAUJUGUGUACUGGGCU	2771
20163	GAAACUGACUUUCUCGAGC	1121	20163	GAAACUGACUUUCUCGAGC	1121	20181	GCUCGAGAAAUGCAGUUUC	2772
20181	CUCGCUAUGGAUUAUC	1122	20181	CUCGCUAUGGAUUAUC	1122	20199	UGAAUJCAUCUAGCGAG	2773
20199	AUACAGCGAAUJAAGCUCG	1123	20199	AUACAGCGAAUJAAGCUCG	1123	20217	CGAGCUUAAAUCGGCU	2774
20217	GAAGGGCUAUGCCUUCGGAC	1124	20217	GAAGGGCUAUGCCUUCGGAC	1124	20235	GUUJGAAGGGCUAGCCCUC	2775
20235	CACAUUCGUUJGUAGGAGAU	1125	20235	CACAUUCGUUJGUAGGAGAU	1125	20253	AAUCUCUAAAACGAUGUG	2776
20253	UUCAGUUAUGGAGACAUUJG	1126	20253	UUCAGUUAUGGAGACAUUJG	1126	20271	CAAGGUUGUCCAUJGACUGAA	2777
20271	GGGGGUUCUJGUUAAAUGA	1127	20271	GGGGGUUCUJGUUAAAUGA	1127	20289	UCAUJUAAAUGGAAGCCGCC	2778
20289	AUAGGGCUUAGCCAAGGCCU	1128	20289	AUAGGGCUUAGCCAAGGCCU	1128	20307	AGGGCUUAGGCCUAGGCCU	2779

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20307	UCACAAGAUUCACCAUUA	1129	20307	UCACAAGAUUCACCAUUA	1129	20325	UAAGUGGGUGAAUCUUGUGA	2780
20325	AAAUUAGAGGAUUUAUCC	1130	20325	AAAUUAGAGGAUUUAUCC	1130	20343	GGAUAAAUCUCUCAUAAA	2781
20343	CCUAUGGACAGCACGUGA	1131	20343	CCUAUGGACAGCACGUGA	1131	20361	UCACUGGCGUGGUCCAUAGG	2782
20361	AAAAAUUACUUCUAAACAG	1132	20361	AAAAAUUACUUCUAAACAG	1132	20379	CUGUUAGAAGAUUUUUUU	2783
20379	GAUGGCCAACAGGUUCAU	1133	20379	GAUGGCCAACAGGUUCAU	1133	20397	AUGAACCUUGGUUGGCCAAC	2784
20397	UCAAAAAUGUGUUGGUUCUG	1134	20397	UCAAAAAUGUGUUGGUUCUG	1134	20415	CAGAACACACACAUUUUGA	2785
20415	GUGAUUGAUUCUUUACUUG	1135	20415	GUGAUUGAUUCUUUACUUG	1135	20433	CAAGUAAAAGAUCAAUCAC	2786
20433	GAUGACUUGUGCAGGAAUA	1136	20433	GAUGACUUGUGCAGGAAUA	1136	20451	UAUCUCGACAAAGUCAUC	2787
20451	AUAAAUGUACAAAGAUUGU	1137	20451	AUAAAUGUACAAAGAUUGU	1137	20469	ACAAAUUCUUGUGACUUUAU	2788
20469	UCAGUGAUUUCUAAAAGUGG	1138	20469	UCAGUGAUUUCUAAAAGUGG	1138	20487	CCACUJJUJUGAAAUCACUGA	2789
20487	GUCAAGGUUACAUUUGACU	1139	20487	GUCAAGGUUACAUUUGACU	1139	20505	AGUCAAUUGUAACCUCUUGAC	2790
20505	UAUGCUGAAUUCUUCUUCU	1140	20505	UAUGCUGAAUUCUUCUUCU	1140	20523	UGAAUAAAUCAGCAUA	2791
20523	AUGCUUUGGUUGGUAGGAUG	1141	20523	AUGCUUUGGUUGGUAGGAUG	1141	20541	CAUCUJUAGCAGCAAAGCAU	2792
20541	GCACAUUGUUGAAACCUUCU	1142	20541	GCACAUUGUUGAAACCUUCU	1142	20559	AGAAAGGUUJUACAUGUCC	2793
20559	UACCCCCAAACUACAAGCA	1143	20559	UACCCCCAAACUACAAGCA	1143	20577	UUGCUUUGGUUGGUUGGUUA	2794
20577	AGUCGAGGGUGGCCAACAG	1144	20577	AGUCGAGGGUGGCCAACAG	1144	20595	CGUGGUCCACGCUUGACU	2795
20595	GUGUJUGGGAUGCUACU	1145	20595	GUGUJUGGGAUGCUACU	1145	20613	AGUJAGGCAUGCAACACC	2796
20613	UUGUACAAGAUUGCAAGAA	1146	20613	UUGUACAAGAUUGCAAGAA	1146	20631	UUCUJUJGCAUCUUGUACAA	2797
20631	AUGCUUCUJUGAAAAAGUG	1147	20631	AUGCUUCUJUGAAAAAGUG	1147	20649	CACACUJJUJUCAAGAACAU	2798
20649	GAxCCUUCAGAAUJAUGUG	1148	20649	GAxCCUUCAGAAUJAUGUG	1148	20667	CACCAJAAUUCUGAAGGGUC	2799
20667	GGAAAUGGUUGGUUACCAA	1149	20667	GGAAAUGGUUGGUUACCAA	1149	20685	UUGGUUAACAGCAUUUUC	2800
20685	AAAGGAAUUAUGAUAGAUG	1150	20685	AAAGGAAUUAUGAUAGAUG	1150	20703	CAUJUCAUJUUAUCCUUU	2801
20703	JUGGCCAAAGUAIACUAAAC	1151	20703	JUGGCCAAAGUAIACUAAAC	1151	20721	GUJUGAUUACUJJUGCGAC	2802
20721	CUGUGUCAAAUACUAAAUA	1152	20721	CUGUGUCAAAUACUAAAUA	1152	20739	UAUUAUAGUAUJGACACAG	2803
20739	ACACUUACUUUAGCUGUAC	1153	20739	ACACUUACUUUAGCUGUAC	1153	20757	GUACAGCUAAAAGUAAGGU	2804
20757	CCCUUACAAACUAGAGUUA	1154	20757	CCCUUACAAACUAGAGUUA	1154	20775	UAACUCUCAUJUUGGUAGGG	2805
20775	AUUCACUUUGGUUGGUUGCU	1155	20775	AUUCACUUUGGUUGGUUGCU	1155	20793	AGCCAGCACCAGUAAU	2806
20793	UCUGAUAAAAGGUUGGUUG	1156	20793	UCUGAUAAAAGGUUGGUUG	1156	20811	GUCCGAAUCUUCUUAUCAGA	2807
20811	CCAGGUACAGGUUGGUUGCUA	1157	20811	CCAGGUACAGGUUGGUUGCUA	1157	20829	UGAGCAGCAGGUUGGUUGGG	2808
20829	AGACAAUGGUUGGCCAACUG	1158	20829	AGACAAUGGUUGGCCAACUG	1158	20847	CAGUJGGCAACCAUUGUCU	2809
20847	GGCACACUUCUJUGGUUGAU	1159	20847	GGCACACUUCUJUGGUUGAU	1159	20865	AAUAGCAGCAGGUUGGGCC	2810
20865	UCAGAUUCUUAUGACUUCG	1160	20865	UCAGAUUCUUAUGACUUCG	1160	20883	CGAAAGCUUUAAGAUUCUGA	2811
20883	GUUCUCCGACGCCAUUUCUA	1161	20883	GUUCUCCGACGCCAUUUCUA	1161	20901	UAGAAUUAUGCGUGGGAGAC	2812
20901	ACUUUUAUUGGAGACUGUG	1162	20901	ACUUUUAUUGGAGACUGUG	1162	20919	CACAGUCUCCAAUAAAAGU	2813
20919	GCAACAGUACAUACGGCUA	1163	20919	GCAACAGUACAUACGGCUA	1163	20937	UAGCCGUUAUGGUACUGUUC	2814
20937	AUAAAUGGGGACCUUUA	1164	20937	AUAAAUGGGGACCUUUA	1164	20955	UAUUAAGGUUGCCAUUUAU	2815
20955	AUUAGCGAUAGUAGAC	1165	20955	AUUAGCGAUAGUAGAC	1165	20973	GGUCAUACAUUAUCGCUUAA	2816
20973	CCUAGGACCAAAACAUUGA	1166	20973	CCUAGGACCAAAACAUUGA	1166	20991	UCACAUJGUUUUGGUCCUAGG	2817
20991	ACAAAAGAGAAUGACUCUA	1167	20991	ACAAAAGAGAAUGACUCUA	1167	21009	UAGAGCUUUCUUCUUCUUG	2818
21009	AAAGAAGGGGUUUUCACUU	1168	21009	AAAGAAGGGGUUUUCACUU	1168	21027	AAGGUAAAACCCUUUCUUG	2819
21027	UAUCUGUGGUUGGUUUUA	1169	21027	UAUCUGUGGUUGGUUUUA	1169	21045	UUAUAAAUCACAGAUAA	2820
21045	AAGCAAAACUAGCCUGG	1170	21045	AAGCAAAACUAGCCUGG	1170	21063	CCAGGGCUAUGUUUGGUUU	2821

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21063	GGUGGUUCUAGCUGUAA	1171	21063	GGUGGUUCUAGCUGUAA	1171	21081	UUACAGCUAUAGAACCCACC	2822
21081	AGAUAAACAGGCAUUCU	1172	21081	AAGAUAAACAGGCAUUCU	1172	21099	AGAAUAGCUCUGUUAUCU	2823
21099	UGGAUAGCUGACCUUACA	1173	21099	UGGAUAGCUGACCUUACA	1173	21117	UGUAAAAGCUGACCUUACA	2824
21117	AAGCUUAUGGGCCAUUCU	1174	21117	AAGCUUAUGGGCCAUUCU	1174	21135	AGAAUAGGCCAUAGCUU	2825
21135	UCAUGGUGGGACAGCUUUG	1175	21135	UCAUGGUGGGACAGCUUUG	1175	21153	CAAAAGCUGUCGCCAUAGCU	2826
21153	GUACAAAUGUAAGCAU	1176	21153	GUACAAAUGUAAGCAU	1176	21171	AUGCAUJJUACAUJGUUAAC	2827
21171	UCAUCAUCGGAAAGCAU	1177	21171	UCAUCAUCGGAAAGCAU	1177	21189	AAAAUAGCUCUGGAUGAUGA	2828
21189	UUAUUGGGCUAACAUAC	1178	21189	UUAUUGGGCUAACAUAC	1178	21207	GAUAGGUAGGCCAACAUAAA	2829
21207	CUUGCCAAGCGGAAGAAC	1179	21207	CUUGCCAAGCGGAAGAAC	1179	21225	GUUCCUUCGGCUUGCCAAAG	2830
21225	CAAUUGAUGGCUAUACCA	1180	21225	CAAUUGAUGGCUAUACCA	1180	21243	UGGUUAUGCCAUCAUUUG	2831
21243	AUGCAUGCUACUACAUU	1181	21243	AUGCAUGCUACUACAUU	1181	21261	AAAUGUAGUUAUGCAU	2832
21261	UUCUGGAGGAACACAAUC	1182	21261	UUCUGGAGGAACACAAUC	1182	21279	GAUJJUGGUUCUCCAGAA	2833
21279	CCUAUCCAGUUGCUUCCU	1183	21279	CCUAUCCAGUUGCUUCCU	1183	21297	AGGAAGACAACUGGUAAGG	2834
21297	UAUUCACUCUJUGACAU	1184	21297	UAUUCACUCUJUGACAU	1184	21315	UCAUJGUCAAGAGUGAAUA	2835
21315	AGCAAAUUCUCCUJAAU	1185	21315	AGCAAAUUCUCCUJAAU	1185	21333	AUUJAGAGGAAUJGUUGCU	2836
21333	UUAAGAGGAACUGCUUAA	1186	21333	UUAAGAGGAACUGCUUAA	1186	21351	UJACAGCAGGUUCUCCUUA	2837
21351	AUGUCUCLUJAAGGAAUC	1187	21351	AUGUCUCLUJAAGGAAUC	1187	21369	GAUJUCUCCUUAAGGACAU	2838
21369	CAAUCAUAGAUAAUGAUU	1188	21369	CAAUCAUAGAUAAUGAUU	1188	21387	AAAUCAUACAUJGUAUUUG	2839
21387	UAUUCUCUJUGGAAAAAG	1189	21387	UAUUCUCUJUGGAAAAAG	1189	21405	CJJUJJCCAGAAGAGAAUA	2840
21405	GUAGGGCUUACAUJAGAG	1190	21405	GUAGGGCUUACAUJAGAG	1190	21423	CUCUAAUGAUAAGCCUACC	2841
21423	GAAAACAACAGAGUUGGG	1191	21423	GAAAACAACAGAGUUGGG	1191	21441	CCACAAUCUCUGUJGUUUUC	2842
21441	GUUCAAGUGAUUUUCUUG	1192	21441	GUUCAAGUGAUUUUCUUG	1192	21459	CAAGAAUUAUCACUJUGAAAC	2843
21459	GUUACAACUAAAAGAAC	1193	21459	GUUACAACUAAAAGAAC	1193	21477	UGUUCGUUAGGUUGGUUAC	2844
21477	AUGUUUAUJUCUJAU	1194	21477	AUGUUUAUJUCUJAU	1194	21495	AUAAUAGAAAUAACAU	2845
21495	UUUCUUAUCUJCACUAGUG	1195	21495	UUUCUUAUCUJCACUAGUG	1195	21513	CACUJAGAGGAGUAAGAAA	2846
21513	GUAGGUAGCCUJGACGGU	1196	21513	GUAGGUAGCCUJGACGGU	1196	21531	ACCGGUICAAGGUACUACC	2847
21531	UGCACCAUCUJUGAUGAUG	1197	21531	UGCACCAUCUJUGAUGAUG	1197	21549	CAUCAUCAAAAGUGGGUGCA	2848
21549	GUUAAGCUCUAAAUCUA	1198	21549	GUUAAGCUCUAAAUCUA	1198	21567	UGUAUJUAGGCUUGUAAC	2849
21567	ACUCAACAUACUUCAUCA	1199	21567	ACUCAACAUACUUCAUCA	1199	21585	UAGAUAGAUJGUUGUGAGU	2850
21585	AUGAGGGGGGUUACUAUC	1200	21585	AUGAGGGGGGUUACUAUC	1200	21603	GAUJGUAAACCCCCCUAU	2851
21603	CCUGAUGAAAUUUJAGAU	1201	21603	CCUGAUGAAAUUUJAGAU	1201	21621	AUCUAAAAAUUUCAUCAUGG	2852
21621	UCAGACACUCUJAUJUA	1202	21621	UCAGACACUCUJAUJUA	1202	21639	UAAAAGAGGUUGUGUGUGA	2853
21639	ACUCAGGAAUJAUJUUJUC	1203	21639	ACUCAGGAAUJAUJUUJUC	1203	21657	GAAGAAUAAAUCUCCUGGU	2854
21657	CAUAAAUAUUCUAUJUA	1204	21657	CAUAAAUAUUCUAUJUA	1204	21675	UAACAUUAJAGAAJAAUJGG	2855
21675	ACAGGGUUCUJAUJUA	1205	21675	ACAGGGUUCUJAUJUA	1205	21693	UAAAAGUAGAAACCCJGU	2856
21693	AUCAUACGUUJGGCAACC	1206	21693	AUCAUACGUUJGGCAACC	1206	21711	GGUJGCCAAGGUAGAUU	2857
21711	CCUGCUAUACCUUUJUAGG	1207	21711	CCUGCUAUACCUUUJUAGG	1207	21729	CCUJUAAAAGGUAGACAGG	2858
21729	GAUGGUAAUJAUJUUJUCUG	1208	21729	GAUGGUAAUJAUJUUJUCUG	1208	21747	CAGCAJAAAUAUACCAUC	2859
21747	GCCACAGAGAAAUAUJUA	1209	21747	GCCACAGAGAAAUAUJUA	1209	21765	CAUJUGAUJUUUCUJUGGGC	2860
21765	GUUGUCGGGUUGGGUUU	1210	21765	GUUGUCGGGUUGGGUUU	1210	21783	AAACCCAACCACGGACAAC	2861
21783	UUUGGUUCUACCAUGAACA	1211	21783	UUUGGUUCUACCAUGAACA	1211	21801	UGUUCAGGUAGAACAAA	2862
21801	AACAAGUCACAGUGGUGA	1212	21801	AACAAGUCACAGUGGUGA	1212	21819	UACCGCACUGUACUUGUU	2863

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21819	AUUAUAAUAAACAUUCUA	1213	21819	AUUAAAUAACAAUUCUA	1213	21837	UAGAAUUGUUAAAUAUAU	2864
21837	ACUAAUGUGUUAAUCGAG	1214	21837	ACUAAUGUGUUAAUCGAG	1214	21855	CUCGUAAAACAUCUUAGU	2865
21855	GCAUGUAAKCUUUGAAUUGU	1215	21855	GCAUGUAAKCUUUGAAUUGU	1215	21873	ACAUUUCAAAUGUACUGC	2866
21873	UGUGACAACCCUUUCUUG	1216	21873	UGUGACAACCCUUUCUUG	1216	21891	CAAAGAAAGGGGUUGUCACA	2867
21891	GCUGUUUUCUAAAACCCAU	1217	21891	GCUGUUUUCUAAAACCCAU	1217	21909	CCAUUGGUUUGAAAACAGC	2868
21909	GGUACACAGACACAUACUA	1218	21909	GGUACACAGACACAUACUA	1218	21927	UAGUAUGUGUCUGUGUAC	2869
21927	AUGAUAAUUCGAAUAAUGAU	1219	21927	AUGAUAAUUCGAAUAAUGAU	1219	21945	AUGCAUUAUCGAAUAAUCAU	2870
21945	UUUAUAAUUCGACAUUUCAGU	1220	21945	UUUAUAAUUCGACAUUUCAGU	1220	21963	ACUUGAAAAGGGCAUAAA	2871
21963	UACAUAAUCLGAUGGCCUUU	1221	21963	UACAUAAUCLGAUGGCCUUU	1221	21981	AAAAGGGCAUCAUGAUAGUA	2872
21981	UCGCUJUGAUGUUUCAGAA	1222	21981	UCGCUJUGAUGUUUCAGAA	1222	21999	UUUCUGAAAACAUCAAGCGA	2873
21999	AAGUCAGGUAAAUAAC	1223	21999	AAGUCAGGUAAAUAAC	1223	22017	GUUUAAAUAUACCUGACUU	2874
22017	CACUACGAGAGUUUGUGU	1224	22017	CACUACGAGAGUUUGUGU	1224	22035	ACACAAACUCUGGUAGUG	2875
22035	UUUUAAAUAAGAUGGGU	1225	22035	UUUUAAAUAAGAUGGGU	1225	22053	ACCCAUUCUUUAUUUUAAA	2876
22053	UUUCUCUUAUGUUUAAGG	1226	22053	UUUCUCUUAUGUUUAAGG	1226	22071	CCUUUAUAAAACAUAGAGAA	2877
22071	GGCUAAUCAACCUGAUAGU	1227	22071	GGCUAAUCAACCUGAUAGU	1227	22089	CAUCUAGGGUUGUGAUAGCC	2878
22089	GUAGUICCGUGAUCAUCU	1228	22089	GUAGUICCGUGAUCAUCU	1228	22107	AAGGGUAGUACGACAUAC	2879
22107	UCUGGUUUUAACAUUGUA	1229	22107	UCUGGUUUUAACAUUGUA	1229	22125	UCAAGUGUAAAAGGAGA	2880
22125	AAACCUAAUUUUAAGUUGC	1230	22125	AAACCUAAUUUUAAGUUGC	1230	22143	GCAACIUUAAAUAAGGUU	2881
22143	CCUCUJGGJAUUACAUUA	1231	22143	CCUCUJGGJAUUACAUUA	1231	22161	UAUGUJAUUACCAAGAGG	2882
22161	ACAAAUUUUAGGCCAUUC	1232	22161	ACAAAUUUUAGGCCAUUC	1232	22179	GAUUGGCUCUAAAUAUGU	2883
22179	CUUACAGCCUUUCACUG	1233	22179	CUUACAGCCUUUCACUG	1233	22197	CAGGUGAAAAGCUGUAG	2884
22197	GCUCUAAAGACAUUUGGGCA	1234	22197	GCUCUAAAGACAUUUGGGCA	1234	22215	UGCCCCAAAUGCUUAGGC	2885
22215	ACGUCAGCUCGCCUAAU	1235	22215	ACGUCAGCUCGCCUAAU	1235	22233	AAUAGGCUGCGCCUGACGU	2886
22233	UUUGUUGGCCUAAAAGC	1236	22233	UUUGUUGGCCUAAAAGC	1236	22251	GCUUUAAAUGCCAACAAA	2887
22251	CCAACUACAUUAUAGCUCA	1237	22251	CCAACUACAUUAUAGCUCA	1237	22269	UGAGCAUAAAUGGUAGUGG	2888
22269	AAGUAUGAIGAAAUGUA	1238	22269	AAGUAUGAIGAAAUGUA	1238	22287	UACCAUUUCAUCAUACUU	2889
22287	ACAAUCACAGAUGCUUG	1239	22287	ACAAUCACAGAUGCUUG	1239	22305	CAACAGCAUCUGUGAUUGU	2890
22305	GAUUGUJCUCAAAUCAC	1240	22305	GAUUGUJCUCAAAUCAC	1240	22323	GUGGAUUGGAAACAUC	2891
22323	CUUGCGUACUCAAAUGCU	1241	22323	CUUGCGUACUCAAAUGCU	1241	22341	AGCAUJJGAGUUGAGCAAG	2892
22341	UCUGUUAAGAGCUUJGAGA	1242	22341	UCUGUUAAGAGCUUJGAGA	1242	22359	UCUCAAAAGCUUACACAGA	2893
22359	AUUGACAAGGAAUUCUAC	1243	22359	AUUGACAAGGAAUUCUAC	1243	22377	GGUAAAUCUUCUUGUCAAU	2894
22377	CAGACCUCUAAUUCAGGG	1244	22377	CAGACCUCUAAUUCAGGG	1244	22395	CCCUUGAAAAGGGUCUG	2895
22395	GUUGUUCCCUCAGGGAUG	1245	22395	GUUGUUCCCUCAGGGAUG	1245	22413	CAUCUUCAGGGAAUCUACAC	2896
22413	GUUGUGAGAUUCCCUUAUA	1246	22413	GUUGUGAGAUUCCCUUAUA	1246	22431	UAUJAGGGAAUCUACAC	2897
22431	AUUACAAAACUUGUGUCUU	1247	22431	AUUACAAAACUUGUGUCUU	1247	22449	AAGGGACACAAGGUUGUAAU	2898
22449	UUGGGAGGGUUUUUAUG	1248	22449	UUGGGAGGGUUUUUAUG	1248	22467	CAUAAAACCUUCUCCAAA	2899
22467	GUACUAAAUCUUCUJUG	1249	22467	GUACUAAAUCUUCUJUG	1249	22485	CAGAGGGAAUUAUGUAGC	2900
22485	GUCUAUGCAJGGGAGA	1250	22485	GUCUAUGCAJGGGAGA	1250	22503	UUCUCUCCCCAUGCAUAGC	2901
22503	AAAAAAAUAUUCUAAUJUG	1251	22503	AAAAAAAUAUUCUAAUJUG	1251	22521	CACAAUJAGAAAUAUUUU	2902
22521	GUUGCUGAUUACUCUGGC	1252	22521	GUUGCUGAUUACUCUGGC	1252	22539	GCACAGGUAAAUCAGCAAC	2903
22539	CUCUACACUCAACAUUU	1253	22539	CUCUACACUCAACAUUU	1253	22557	AAAAGUGGUUGGUAGAG	2904
22557	UUUUCACCUUUAAGGGCU	1254	22557	UUUUCACCUUUAAGGGCU	1254	22575	AGCACUAAAAGGUAAAAA	2905

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22575	UAGGGCGUUUCGCCACUA	1255	22575	UAUGGGGUUUCGCCACUA	1255	22593	UAGGGCAGAACGCCAUA	2906
22593	AAGUUGAAUIGAUUJGGCU	1256	22593	AAGUUGAAUAGAUCLJJIGCU	1256	22611	AGCAAGAGAUCAUJCAACUU	2907
22611	UUCUCCAAUIGCUAUGCAG	1257	22611	UUCUCCAAUUGUCUAVUGCAG	1257	22629	CUGGCAUAGACAUUJGGAGAA	2908
22629	GAUUCUUJGUAGUCAAGG	1258	22629	GAUUCUUUUGGUAGUCAAGG	1258	22647	CCUJGACUCAAAAGAAUC	2909
22647	GAGAUGAUGAAAGAAA	1259	22647	GGAGAUGAUGUAGAACAAA	1259	22665	UJJUGCUUCAUCAUCAUCUU	2910
22665	AUAGGCAGCCAGGACAAACUG	1260	22665	AUAGGCAGCCAGGACAAACUG	1260	22683	CAGUJJUGGUUJGGGUCCUAI	2911
22683	GGUGUUAUJGUCAUUAUA	1261	22683	GGUGUUAUJGUCAUUAUA	1261	22701	UAUAUCAGCAUAAACACC	2912
22701	AUUUAUAAAUGGCCAGAUG	1262	22701	AUUUAUAAAUGGCCAGAUG	1262	22719	CAUCUGGCAAUUAUAUAUU	2913
22719	GAUUCUAGGGGUUGGUCC	1263	22719	GAUUCUAGGGGUUGGUCC	1263	22737	GGACAACCCAUAGAAAC	2914
22737	CUUGCUUJGGAUACUAGGA	1264	22737	CUUGCUUJGGAUACUAGGA	1264	22755	UCCUJGUUAUJCACGCAAG	2915
22755	AACAUUAGAUGCUACUJCAA	1265	22755	AACAUUAGAUGCUACUJCAA	1265	22773	UJGAAUJGUAGCAUCAUGU	2916
22773	ACUGGUUAUUAUUAUUAU	1266	22773	ACUGGUUAUUAUUAUUAU	1266	22791	UAUAUUAUUAUUAUACCAGU	2917
22791	AAUUAUAGGUAAUCUJGAC	1267	22791	AAUUAUAGGUAAUCUJGAC	1267	22809	GUICUAGAUACCUAUUAUU	2918
22809	CAUGGCAGCUUAGGCCU	1268	22809	CAUGGCAGCUUAGGCCU	1268	22827	AGGGCUUAGGUUJGGCCAU	2919
22827	UUUGAGAGAGACAUUCUA	1269	22827	UUUGAGAGAGACAUUCUA	1269	22845	UAGGUAGUJGUUCUCCUAAA	2920
22845	AUAGUGGCCUUUCUCCUG	1270	22845	AUAGUGGCCUUUCUCCUG	1270	22863	CAGGGGAGAAAGGCACAUU	2921
22863	GAUGGCAAACCUUGCCCC	1271	22863	GAUGGCAAACCUUGCCCC	1271	22881	GGGUCAAGGUUJGGCCAU	2922
22881	CCACCGCUUAAAUGUU	1272	22881	CCACCGCUUAAAUGUU	1272	22899	AAACAUUAGGAGGAGGG	2923
22899	UAUUGGCCAUUAAAUGAUU	1273	22899	UAUUGGCCAUUAAAUGAUU	1273	22917	AAUCAUUIJGUUGCCAAUA	2924
22917	UAUGGUUUUJUACACCACUA	1274	22917	UAUGGUUUUJUACACCACUA	1274	22935	UAGUGGUUGUAAAACCAUA	2925
22935	ACUGGCAGUJGGCUACCAAC	1275	22935	ACUGGCAGUJGGCUACCAAC	1275	22953	GUJGUAGGCCAUJGGCCAU	2926
22953	CCUUACAGAUJGUUJGUAC	1276	22953	CCUUACAGAUJGUUJGUAC	1276	22971	GUACUACACUJGUUAGG	2927
22971	CUUUCUJUJIGAAUCUUUA	1277	22971	CUUUCUJUJIGAAUCUUUA	1277	22989	UJAAUAGUJGUUAAAAGAAAG	2928
22989	AUGGACCGGCCACGGUUU	1278	22989	AUGGACCGGCCACGGUUU	1278	23007	AAACCGUGGGCCGGGUCCAUU	2929
23007	UGGGACCAAAAUUAUCCA	1279	23007	UGGGACCAAAAUUAUCCA	1279	23025	UGGAAUAAAUGGUCCACAA	2930
23025	ACUGACCUUJUAGAACCC	1280	23025	ACUGACCUUJUAGAACCC	1280	23043	GGUICUJUAAAAGGUCAJGU	2931
23043	CAUGUGGUCAUJUUAUJU	1281	23043	CAUGUGGUCAUJUUAUJU	1281	23061	AAUJAAAUIUJGUACACACUG	2932
23061	UUAAAUGGACUCACUGUA	1282	23061	UUAAAUGGACUCACUGUA	1282	23079	UACCGUGAGGUCCAUAAA	2933
23079	ACUGGUGGUJUACUCUU	1283	23079	ACUGGUGGUJUACUCUU	1283	23097	AAGGGGUUAAACACACCCAGU	2934
23097	UCUUCAAGAGAUJUCAAC	1284	23097	UCUUCAAGAGAUJUCAAC	1284	23115	GUJGAAUJCUUUJGUAGAA	2935
23115	CCAUUCAACAUUJGUCC	1285	23115	CCAUUCAACAUUJGUCC	1285	23133	GGCCAAAUGGUUAGG	2936
23133	CGUGAUGUUJUCGUUUCA	1286	23133	CGUGAUGUUJUCGUUUCA	1286	23151	UGAAUACUJGUAAUCACUG	2937
23151	ACUGAUUCCGUUCGAGAU	1287	23151	ACUGAUUCCGUUCGAGAU	1287	23169	GAUCUGGAACGGAAUCAGU	2938
23169	CUAAAAACAUUCUGAAAUAU	1288	23169	CUAAAAACAUUCUGAAAUAU	1288	23187	AUAUUCAGAUJGUUUUAGG	2939
23187	UAGACAUUJUCGUJGCG	1289	23187	UAGACAUUJUCGUJGCG	1289	23205	CGCAAGGUAAAUGUCUAA	2940
23205	GCUUUUGGGGUJGUAGUG	1290	23205	GCUUUUGGGGUJGUAGUG	1290	23223	CACUJUACCCCCAAAAGC	2941
23223	GUAAAUAACCCUGGAACAA	1291	23223	GUAAAUAACCCUGGAACAA	1291	23241	UJGUUJCCAGGUUAAUJAC	2942
23241	AUGGUUCAUCUJGUAGUG	1292	23241	AUGGUUCAUCUJGUAGUG	1292	23259	CAACUUCAGAUJGUAGAC	2943
23259	GCUGUUCAUJCAAGAUG	1293	23259	GCUGUUCAUJCAAGAUG	1293	23277	CAUCUUGAUJGUAGUACAGC	2944
23277	GUAAACUGACUJGUAGUUU	1294	23277	GUAAACUGACUJGUAGUUU	1294	23295	AAACAUCAUGGUAGGUUAC	2945
23295	UCUACAGCAAUUCAUCAG	1295	23295	UCUACAGCAAUUCAUCAG	1295	23313	CUGCAUJGUAAUJGUAGUAG	2946
23313	GAUCAACUCACACCAGCUU	1296	23313	GAUCAACUCACACCAGCUU	1296	23331	AAGGUUGGUJGUAGUAGU	2947

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23331	UGGGCAUUAUUCUACUG	1297	23331	UGGGCAUUAUUCUACUG	1297	23349	CAGUAGAAUUAUUGGCCA	2948
23349	GAAAACAUGUAUUCAGA	1298	23349	GGAAAACAUGUAUUCAGA	1298	23367	UCUGGAAUUAUUGUUUCC	2949
23367	ACUCAAGCGGCGUCUUA	1299	23367	ACUCAAGCGGCGUCUUA	1299	23385	UAAGGAAGGCCUGCUUAGAU	2950
23385	AUAGGAGCJUGGCAUGUCG	1300	23385	AUAGGAGCJUGGCAUGUCG	1300	23403	CGACAUUGCUCAGGCCUGCUU	2951
23403	GACACUUCUJAUGAGGCG	1301	23403	GACACUUCUJAUGAGGCG	1301	23421	CGACACUCAUAGGAAGUGUC	2952
23421	GACAUUCCAUJGGAGCUG	1302	23421	GACAUUCCAUJGGAGCUG	1302	23439	CAGCUCUCCAUJGGAGCUG	2953
23439	GCACAUUJGGCUAGUACC	1303	23439	GCACAUUJGGCUAGUACC	1303	23457	GGUAAUCUAGCACAAUUGCC	2954
23457	CAUACAGUUUCUUAUAC	1304	23457	CAUACAGUUUCUUAUAC	1304	23475	GUAAJAAAGAACUGUAUG	2955
23475	CGUAGUACJAGCCAAAAU	1305	23475	CGUAGUACJAGCCAAAAU	1305	23493	AUJJUJGGCUAGUACUACG	2956
23493	UCUAUUGGGCUUAUCUA	1306	23493	UCUAUUGGGCUUAUCUA	1306	23511	UAGLUAIAAGGCCACAAUAGA	2957
23511	AUGUCUUUAUGGGCUUGAU	1307	23511	AUGUCUUUAUGGGCUUGAU	1307	23529	UAUCAGGCCCUAAAAGACAU	2958
23529	AGUCAAUUGCUUACUCUA	1308	23529	AGUCAAUUGCUUACUCUA	1308	23547	UAGLUAIAAGGCCACAAUAGACU	2959
23547	AUAUACCAUUGCUUAUC	1309	23547	AUAUACCAUUGCUUAUC	1309	23565	GUAAJGAAUGGUUAUJ	2960
23565	CCUACUAAACUJUUCAUUA	1310	23565	CCUACUAAACUJUUCAUUA	1310	23583	UAAUIGGAAAAGUJUGUAGG	2961
23583	AGCAUUAUCUACAGAUAA	1311	23583	AGCAUUAUCUACAGAUAA	1311	23601	UACUUCUJUGUAGGUAAUGCU	2962
23601	AUGCCUGUUUCUAGGCCA	1312	23601	AUGCCUGUUUCUAGGCCA	1312	23619	UAGCCCAUAGAACAGGCCAU	2963
23619	AAAACCUCCGUAGAUUGUA	1313	23619	AAAACCUCCGUAGAUUGUA	1313	23637	UACAAUCUACGGAGGUUJ	2964
23637	AUAUAGUACAUUCUGGGAG	1314	23637	AUAUAGUACAUUCUGGGAG	1314	23655	CUCCGAGAUGGUACAUUU	2965
23655	GAUUCUACUGAAUGUGCUA	1315	23655	GAUUCUACUGAAUGUGCUA	1315	23673	UAGCACAUCUJAGUAGAAUC	2966
23673	AUUUUGCUUCUCCAAUUAUG	1316	23673	AUUUUGCUUCUCCAAUUAUG	1316	23691	CAUAUIGGAGAACAAUUAU	2967
23691	GUAGCJUJJUGCACACAC	1317	23691	GUAGCJUJJUGCACACAC	1317	23709	GUJUGUGGCAAAAGCUACC	2968
23709	CUAAAUGGUCCACUGAC	1318	23709	CUAAAUGGUCCACUGAC	1318	23727	CUGAGAGGUCCACGUUUAQ	2969
23727	GUUAUUGGUCCUGUACAGG	1319	23727	GUUAUUGGUCCUGUACAGG	1319	23745	CCUUGUUCAGGCAAAUACC	2970
23745	GAUCGCAACACACGUAGA	1320	23745	GAUCGCAACACACGUAGA	1320	23763	CUUCACGUGGUUGUGCGAUJC	2971
23763	GUGUUGCGUCAAGUAAAC	1321	23763	GUGUUGCGUCAAGUAAAC	1321	23781	GUJUGACUUGAGCGAACAC	2972
23781	AAAUGUACAAAACCCAA	1322	23781	AAAUGUACAAAACCCAA	1322	23799	UUGGGUUUUGUACAUUJG	2973
23799	ACUUUGAAAAAUUUIUGUG	1323	23799	ACUUUGAAAAAUUUIUGUG	1323	23817	CACCAAAAUUJUCAAAGU	2974
23817	GUUUUUAAAUIUUCACAAA	1324	23817	GUUUUUAAAUIUUCACAAA	1324	23835	UUUGUGAAAAAUUAAAACC	2975
23835	AUAAUACCUGACCCUCUAA	1325	23835	AUAAUACCUGACCCUCUAA	1325	23853	UAGAGGGGUCAUGGUAAUAU	2976
23853	AAGCCAACUAAGGGGUUU	1326	23853	AAGCCAACUAAGGGGUUU	1326	23871	AAGACCAACUJUGGUCCUUA	2977
23871	UUUUUUAGGAGGACACUC	1327	23871	UUUUUUAGGAGGACACUC	1327	23889	AAGACCAACUJUGGUCCUUA	2978
23889	UUUUUUAGGAGGACACUC	1328	23889	UUUUUUAGGAGGACACUC	1328	23907	CGAGUGUGCCACUUCUAAA	2979
23907	GCUGAUGCGUCCUUCAUGA	1329	23907	GCUGAUGCGUCCUUCAUGA	1329	23925	UCAUGAAAGCCAGCAUCAGC	2980
23925	AAGCAAUAGGGAAUGCC	1330	23925	AAGCAAUAGGGAAUGCC	1330	23943	GGCAUUCGCCCAUUAUGCUU	2981
23943	CUAGGUGAUUAUAGCUA	1331	23943	CUAGGUGAUUAUAGCUA	1331	23961	UAGCAUUAUACCUAG	2982
23961	AGAGAUCUAAUUGGCC	1332	23961	AGAGAUCUAAUUGGCC	1332	23979	GGCCACAAAAGAGAUUCU	2983
23979	CAGAAGUUCUAAUGGACUUA	1333	23979	CAGAAGUUCUAAUGGACUUA	1333	23997	UAAGGUCCAUJUGAACUUCUG	2984
23997	ACAGUGUUGCCACCUUCG	1334	23997	ACAGUGUUGCCACCUUCG	1334	24015	GCAGAGGGGUCAACACUGU	2985
24015	CUCACUGAUJAUGAUJG	1335	24015	CUCACUGAUJAUGAUJG	1335	24033	CAAUUAUCAUCAGUGAG	2986
24033	GCUGCCUACACUGCUC	1336	24033	GCUGCCUACACUGCUC	1336	24051	GAGCAGCAGGUAGGGAGC	2987
24051	CUAGUUAUGGGGUACUGCCA	1337	24051	CUAGUUAUGGGGUACUGCCA	1337	24069	UGGCAGUACCUAACUAG	2988
24069	ACUGCUGGAUGGGACAUU	1338	24069	ACUGCUGGAUGGGACAUU	1338	24087	CAAAUGGUCCAUCCAGCAGU	2989

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24087	GGUGCGGGCUGCUUC	1339	24087	GGUGCGGGCUGCUUC	1339	24105	GAAGAGGCCAGGCCACC	2890
24105	CAAAUACCUUUUGCUAUGC	1340	24105	CAAAUACCUUUUGCUAUGC	1340	24123	GCAUAGCCAAAAGGUUUUG	2891
24123	CAAUUGGCAUAUAGGUUCA	1341	24123	CAAUUGGCAUAUAGGUUCA	1341	24141	UGAACCUUUAUGCCAUUUG	2892
24141	AUGGCAUJGGAGGUUACCC	1342	24141	AUGGCAUJGGAGGUUACCC	1342	24159	GGGUACUCCAUUGGUUCAUU	2893
24159	CAAUAGGUUCUCAUGGAGA	1343	24159	CAAUAGGUUCUCAUGGAGA	1343	24177	UCUCAUAGGAACAUUJJUU	2894
24177	AACCAAAAACAAUUCGCGA	1344	24177	AACCAAAAACAAUUCGCGA	1344	24195	UGGGGUUJGUUJJUUGGUU	2895
24195	AACCAAUUUAACAGGCAGA	1345	24195	AACCAAUUUAACAGGCAGA	1345	24213	UCGCCUJGUUAAAUGGUU	2896
24213	AUUAGCUAAUUCAGAAU	1346	24213	AUUAGCUAAUUCAGAAU	1346	24231	AUUCUJGUUJJUUGACUAAU	2897
24231	UCACUUAACACAUCUA	1347	24231	UCACUUAACACAUCUA	1347	24249	UUGAUJGUUGUUAGUGUA	2898
24249	ACUGCAUJGGCAAGCUGC	1348	24249	ACUGCAUJGGCAAGCUGC	1348	24267	GCAAGCUJGGCCAAUGCAGU	2899
24267	CAAGACGUUGUJAAACAGA	1349	24267	CAAGACGUUGUJAAACAGA	1349	24285	UCUGGUUAAAACACGUUUG	3000
24285	AUGGUCAAGCAUAAAACA	1350	24285	AUGGUCAAGCAUAAAACA	1350	24303	UGUUJAUJGUUJGUAGGCAU	3001
24303	ACACUJGUUAAAACACUJA	1351	24303	ACACUJGUUAAAACACUJA	1351	24321	UAGGUJGUUAAAACAGUGU	3002
24321	AGCUCAUJUJUJACGUAA	1352	24321	AGCUCAUJUJUJACGUAA	1352	24339	UUGACCCAAAJJUAGGCU	3003
24339	AUUUCAAGGUUGGUUAAUG	1353	24339	AUUUCAAGGUUGGUUAAUG	1353	24367	CAUJJIAAGCACACUJGUAAA	3004
24357	GUAUCCUJUCGCGACUUG	1354	24357	GUAUCCUJUCGCGACUUG	1354	24375	CAAGUCGCGAAAAGGUUAUC	3005
24375	GUAUAGGUJGGGGAGG	1355	24375	GUAUAGGUJGGGGAGG	1355	24393	CCUCGCCUCGACUUAUC	3006
24393	GUACAAAUUACAGGUUAA	1356	24393	GUACAAAUUACAGGUUAA	1356	24411	UUAACCUJGUUJJUUGUAC	3007
24411	AUUACAGGOAGACUJAAA	1357	24411	AUUACAGGOAGACUJAAA	1357	24429	UUIUGAAGGUUJGUUGGUU	3008
24429	AGCCUUAACCUAUGUAA	1358	24429	AGCCUUAACCUAUGUAA	1358	24447	UUACAUJAGGUUJGUAGGCU	3009
24447	ACACAACAAUACUACGGG	1359	24447	ACACAACAAUACUACGGG	1359	24465	CCUJGUUJGUUJGUUGGUJU	3010
24465	GCUGGUJGUUACGGGUU	1360	24465	GCUGGUJGUUACGGGUU	1360	24483	AAGGCCUGGUUJGUAGGAGC	3011
24483	UCUGCUAAUACUJUCGUCA	1361	24483	UCUGCUAAUACUJUCGUCA	1361	24501	UAGCAGCAAGGUUJGUAGCA	3012
24501	ACUAAAAGUUCUGAGUGUG	1362	24501	ACUAAAAGUUCUGAGUGUG	1362	24519	CACACUJAGACACUJJUAGU	3013
24519	GUUCUJGGACAAUCAAAAA	1363	24519	GUUCUJGGACAAUCAAAAA	1363	24537	UUIUJGUUJGUUJGUAGAAC	3014
24537	AGAGUUGACUJJUGUGAA	1364	24537	AGAGUUGACUJJUGUGAA	1364	24555	UCCACAAAAGUCAACUCU	3015
24555	AAGGGCUACCCUJAUGU	1365	24555	AAGGGCUACCCUJAUGU	1365	24573	ACAUAAAGGUJGUAGGCCUJ	3016
24573	UCCUUCCCACAAAGGCC	1366	24573	UCCUUCCCACAAAGGCC	1366	24591	GGCUGGUJGUUGGGAAAGGA	3017
24591	CGCGAUGGUJGUUGGUUCC	1367	24591	CGCGAUGGUJGUUGGUUCC	1367	24609	GGAAAGACAACCCAUGGG	3018
24609	CUACAUGUACGUAGGUJC	1368	24609	CUACAUGUACGUAGGUJC	1368	24627	GCACAUJCGUGACAUJGUAG	3019
24627	CGACUCCAGGAGGAGACU	1369	24627	CGACUCCAGGAGGAGACU	1369	24645	UUGGUJGGGUJGUUGGUAA	3020
24645	UUCACCCACAGGCCAGCAA	1370	24645	UUCACCCACAGGCCAGCAA	1370	24663	CUUJGUUJGUUJGUACAAAU	3021
24663	AUUUGUCAUGAAGGCCAAG	1371	24663	AUUUGUCAUGAAGGCCAAG	1371	24681	CUUCACGAGGGGUAGUUGGC	3022
24681	GCAUACUOCCUJGUAG	1372	24681	GCAUACUOCCUJGUAG	1372	24699	CUUJACGAGGGGUAGUUGGC	3023
24699	GGUGUUJGUUUJGUUAUG	1373	24699	GGUGUUJGUUUJGUUAUG	1373	24717	CAUAAAACACAAAAACACC	3024
24717	GGCACUUCJGUUJGUUA	1374	24717	GGCACUUCJGUUJGUUA	1374	24735	UAUAAAACCAAGAGUGCC	3025
24735	ACACAGAGGAACUJUUUU	1375	24735	ACACAGAGGAACUJUUUU	1375	24753	AAAAGAAGGUUCUGUGGU	3026
24753	UCUCCACAAAUAUUAUCUA	1376	24753	UCUCCACAAAUAUUAUCUA	1376	24771	UAGUAAAUAUJGUUGGGAGA	3027
24771	ACAGACAAUACAUUJGUUC	1377	24771	ACAGACAAUACAUUJGUUC	1377	24789	AGACAAAUGUJGUUGGUJU	3028
24789	UCAGGAAAUGUUGGUUC	1378	24789	UCAGGAAAUGUUGGUUC	1378	24807	CGACAUACAUUJGUUGGUCA	3029
24807	GUUAUJGGCAUCAUUAACA	1379	24807	GUUAUJGGCAUCAUUAACA	1379	24825	UGUIJAAUJGGCAUUAAC	3030
24825	AACACAGUUUAUGAUCCUC	1380	24825	AACACAGUUUAUGAUCCUC	1380	24843	GAGGAUCUAAAUGUGGUU	3031

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24843	CUGCAACCUGGAGCUUGACU	1381	24843	CUGCAACCUGGAGCUUGACU	1381	24861	AGUCAAAGCCUCUAGGUUGCAG	3032
24861	UCAUUCAAAGGAAGAGCUGG	1382	24861	UCAUUCAAAGGAAGAGCUGG	1382	24879	CCAGCUCUUCUUGGAAUAGA	3033
24879	GACAAGUACUCAAAAUC	1383	24879	GACAAGUACUCAAAAUC	1383	24897	GAUUUUUAGGUACUUGUC	3034
24897	CAUACAUACCCAGAUGUUG	1384	24897	CAUACAUACCCAGAUGUUG	1384	24915	CAACAUUCGGGAUAGUAUG	3035
24915	GAUCUUCGGGACAUUCAG	1385	24915	GAUCUUCGGGACAUUCAG	1385	24933	CUGAAAUGUCGUAAUGCC	3036
24933	GCACAUAAACGCCUUCUGUC	1386	24933	GCACAUAAACGCCUUCUGUC	1386	24951	CGACAGAACGGGUAAUGCC	3037
24951	GUCAACAUUCAAAAAAGAA	1387	24951	GUCAACAUUCAAAAAAGAA	1387	24969	UUUCUUUUAGGUUGUUGAC	3038
24969	AUUGACCGCCUCAAGAGG	1388	24969	AUUGACCGCCUCAAGAGG	1388	24987	CCUCAUUAGGGGGUCAAU	3039
24987	GUCCGCUAAAUIUAAAUG	1389	24987	GUCCGCUAAAUIUAAAUG	1389	25005	CAUJUAAAUIUUGGCAC	3040
25005	GAUUCACUCAUUGACCUUC	1390	25005	GAUUCACUCAUUGACCUUC	1390	25023	GAOGGUCAAUAGAGGAAUIC	3041
25023	CAAGAAUUGGGAAAUIAUG	1391	25023	CAAGAAUUGGGAAAUIAUG	1391	25041	CAUAUUUCCCAAUUCUUG	3042
25041	GAGCAAUAAUAAAUGGC	1392	25041	GAGCAAUAAUAAAUGGC	1392	25059	GCCAUAAAUAUUGCU	3043
25059	CCUUGGUAIGUUGGGUUCG	1393	25059	CCUUGGUAIGUUGGGUUCG	1393	25077	CGAGCCAAAACCAAGG	3044
25077	GGCLUCAUUGCUGGACUAA	1394	25077	GGCLUCAUUGCUGGACUAA	1394	25085	UUAQGUCCAGCAUAGAAGCC	3045
25085	AUUGCCAUCGUCAUGGUUA	1395	25095	AUUGCCAUCGUCAUGGUUA	1395	25113	UAAACCAUGACGAUGGCAAU	3046
25113	ACAAUCUUGGUUJGUUGCA	1396	25113	ACAAUCUUGGUUJGUUGCA	1396	25131	UGCAACAAAGCAAGAUUGU	3047
25131	AUGACUAGUIGUUGGAGUU	1397	25131	AUGACUAGUIGUUGGAGUU	1397	25149	AACUIGCAACACUAGCU	3048
25149	UGCCUCAAGGGGGUGCAUGCU	1398	25149	UGCCUCAAGGGGGUGCAUGCU	1398	25167	AGCAUIGGCCUCCUUGGGCA	3049
25167	UCUUGGGGUUCUUGCGCA	1399	25167	UCUUGGGGUUCUUGCGCA	1399	25185	UGCGAGCAAAACCAAGA	3050
25185	AAGUUUAGGGAUGACU	1400	25185	AAGUUUAGGGAUGACU	1400	25203	AGCUACCUCAUAAAACUU	3051
25203	UCUGAGCCAGUUCUCAAGG	1401	25203	UCUGAGCCAGUUCUCAAGG	1401	25221	CCUJGAGAACGGUCAGA	3052
25221	GGUGUCAAAUUAUACAUUACA	1402	25221	GGUGUCAAAUUAUACAUUACA	1402	25239	UGUAUAAAUAUUGUAGACCU	3053
25239	ACAUAAAACGAACUUAUGGA	1403	25239	ACAUAAAACGAACUUAUGGA	1403	25257	UCCAAUAGUUCGUUUAUGU	3054
25257	AUUUGUUUAUGGAAUUUU	1404	25257	AUUUGUUUAUGGAAUUUU	1404	25275	AAAAAAUCUCAUAAAACAAU	3055
25275	UUACUCUUGGAUCAUUAUC	1405	25275	UUACUCUUGGAUCAUUAUC	1405	25293	GUAAJUGAUCCAAAGUAA	3056
25293	CUGCACAGCCAGUAAAUAU	1406	25293	CUGCACAGCCAGUAAAUAU	1406	25311	AUUIUJUACUGGGUGGGAG	3057
25311	UUGACAAAGCUUCUCCUGC	1407	25311	UUGACAAAGCUUCUCCUGC	1407	25329	GCAGGAGAAAGCAUUGUCAA	3058
25329	CAAGUACUAGUCAUGCUAC	1408	25329	CAAGUACUAGUCAUGCUAC	1408	25347	GUAGCAUAAACAGUACUUG	3059
25347	CAAGCAACGAAUCCCUACUA	1409	25347	CAAGCAACGAAUCCCUACUA	1409	25365	UGVAGGGGUAUUGGUUGUG	3060
25365	AAGCCUCUACUCCCUUCUCCG	1410	25365	AAGCCUCUACUCCCUUCUCCG	1410	25383	CCGAGAGGGAGUAGGGCUU	3061
25383	GAUGGGCUUJGUUJGUUJGU	1411	25383	GAUGGGCUUJGUUJGUUJGU	1411	25401	ACGGCAAAUJAAGGCCAU	3062
25401	UUGCAUUUCUUGCGUUUU	1412	25401	UUGCAUUUCUUGCGUUUU	1412	25419	AAAACAGCAAGAAUUGCAA	3063
25419	UUCAGAGGCGUACCAAAAU	1413	25419	UUCAGAGGCGUACCAAAAU	1413	25437	AUULJUGGUAGGCGUCUGAA	3064
25437	UAAUUGCCGCUAAJAAAG	1414	25437	UAAUUGCCGCUAAJAAAG	1414	25455	CUJJUJUAGGAGGCAUUA	3065
25455	GAUGGGCAGCAGUAGCCCUIUA	1415	25455	GAUGGGCAGCAGUAGCCCUIUA	1415	25473	UAAAGGGCUAGCUGCCAU	3066
25473	AUAAAGGGCUUCCAGUCAU	1416	25473	AUAAAGGGCUUCCAGUCAU	1416	25491	AUGAACUUGGAAAGCCCCUUAU	3067
25491	UUUGCAUUUAUCUGCGCU	1417	25491	UUUGCAUUUAUCUGCGCU	1417	25509	AGCAGCAGUAAUUGCAA	3068
25509	UAUUUUUAGGUACAUUAUC	1418	25509	UAUUUUUAGGUACAUUAUC	1418	25527	GAAUAGGUAGGUACAAUUA	3069
25527	CACAUUCUUCUUCUUCUUC	1419	25527	CACAUUCUUCUUCUUCUUC	1419	25545	GCGACAGCAAGAAAGAUGUG	3070
25545	CGUGCAGGUAGGGGGCGCA	1420	25545	CGUGCAGGUAGGGGGCGCA	1420	25563	UGCCUCUACUACGGGAG	3071
25563	AUUUUUUUAGGUACCUUAUC	1421	25563	AUUUUUUUAGGUACCUUAUC	1421	25581	GCAUAGAGGUACAAUAAAUU	3072
25581	CCUJGAAUAAUUCUACAA	1422	25581	CCUJGAAUAAUUCUACAA	1422	25599	UGUAGAAAAAUUAUCAAAGG	3073

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25599	AUGCAUCAACCCAUGUAG	1423	25599	AAUGCAUCAACGCAUGUAG	1423	25617	CUACAUUGCUGUUGAUGCAU	3074
25617	GAUUUAUUAUGAGAUUUG	1424	25617	GAUUUAUUAUGAGAUUUG	1424	25635	CAACAUUCUCAUAAAUAUC	3075
25635	GCCUUUUGGUAGGGCAA	1425	25635	GCCUUUUGGUAGGGCAA	1425	25653	UGGCACUUCCAAAAGCC	3076
25653	AUUCCAAAGAACCCAUUACU	1426	25653	AUUCCAAAGAACCCAUUACU	1426	25671	AGUAUAGGUUUCUUGGAAU	3077
25671	UUUAUGAUGCCAACUACUU	1427	25671	UUUAUGAUGCCAACUACUU	1427	25689	AAGUAGUUGGUUCAUAAA	3078
25689	UGUUIUUGCUGGCCACACACA	1428	25689	UGUUIUUGCUGGCCACACACA	1428	25707	UGUGUGUGCCAGCAAAACAA	3079
25707	UAUACUAUGACUACUGUAU	1429	25707	UAUACUAUGACUACUGUAU	1429	25725	AUACAGUAGCUAUAGUUAU	3080
25725	UACCAUAUACAGUGUAC	1430	25725	UACCAUAUACAGUGUAC	1430	25743	GUGACACGUUAUAGGUUA	3081
25743	CAGAUACAAUUGGUUAC	1431	25743	CAGAUACAAUUGGUUAC	1431	25761	GUAAAGGACAAUUGGUUACUG	3082
25761	CUGAAGGGUGACGGCAUUC	1432	25761	CUGAAGGGUGACGGCAUUC	1432	25779	AAAUGGCCGUACCUUCAG	3083
25779	CAACACCAAAACUCAAAGA	1433	25779	CAACACCAAAACUCAAAGA	1433	25797	UCUUUGAGUUUUGGUUUG	3084
25797	AGAACUACAAAUGGUUGG	1434	25797	AGAACUACAAAUGGUUGG	1434	25815	CCACCAAAUUGGUACU	3085
25815	GUUAUUCUGGAGGUAGGCA	1435	25815	GUUAUUCUGGAGGUAGGCA	1435	25833	UGCCUACUCCUAGGUAAAC	3086
25833	ACUCAGGUUGGUAAAAGACUA	1436	25833	ACUCAGGUUGGUAAAAGACUA	1436	25851	UAGUCUUCUAAACCCUGAGU	3087
25851	AUGUCGUUGGUACUGGUACUA	1437	25851	AUGUCGUUGGUACUGGUACUA	1437	25869	UAGGCCAUAGUACAAAGACAU	3088
25869	AUUUCACCGAGGUUUAACUA	1438	25869	AUUUCACCGAGGUUUAACUA	1438	25887	UAGUAAAUCUJGGGUAAA	3089
25887	ACCAGGUUGAGGUACACAA	1439	25887	ACCAGGUUGAGGUACACAA	1439	25905	UGUGUAGACUAAAGCUGGU	3090
25905	AAAUUACUACAGACUGG	1440	25905	AAAUUACUACAGACACUGG	1440	25923	CCAGUGUCUGUAGUAAAUI	3091
25923	GUAUUGAAAUGGUACAUU	1441	25923	GUAUUGAAAUGGUACAUU	1441	25941	AAUGUAGGUUUUCAUAC	3092
25941	UCUUCAUUAAAAGGU	1442	25941	UCUUCAUUAAAAGGU	1442	25959	AGCUUUGGUAAAAGGUAGA	3093
25959	UGUUAIAAGGACCCACGAA	1443	25959	UGUUAIAAGGACCCACGAA	1443	25977	UICUGGGGUUCUJUACAA	3094
25977	AUGUGCAAAUACACAAU	1444	25977	AUGUGCAAAUACACAAU	1444	25995	AUUGUGGUAGUUGACACAU	3095
25995	UCGACGGCUUCUUGGAGU	1445	25995	UCGACGGCUUCUUGGAGU	1445	26013	ACUCUGGAAGGCCGUCCGA	3096
26013	UGCUUAUCCAGCAAUGGA	1446	26013	UGCUUAUCCAGCAAUGGA	1446	26031	UCCAUUUGGUAGGUUAGCAA	3097
26031	AUCCAAUUUAUGAGGCC	1447	26031	AUCCAAUUUAUGAGGCC	1447	26049	GCGCUCAUCAUAAAUGGUAU	3098
26049	CGACGACGACUACUAGCGU	1448	26049	CGACGACGACUACUAGCGU	1448	26067	ACGGCUAGUAGGUCCGUCCG	3099
26067	UGCCUUUUGUAGGACAAGA	1449	26067	UGCCUUUUGUAGGACAAGA	1449	26085	UCUJUGGUUCUAAAAGGCA	3100
26085	AAAGUGAGUAGGUACUUA	1450	26085	AAAGUGAGUAGGUACUUA	1450	26103	AUAAGUUGGUACUUCACUU	3101
26103	UGUACUACUUGGUUGGGA	1451	26103	UGUACUACUUGGUUGGGA	1451	26121	UCGGAAAGGAAUAGGUACU	3102
26121	AGAAAACAGGUACGUUAU	1452	26121	AGAAAACAGGUACGUUAU	1452	26139	AUUAACGUACCUUGUUCUU	3103
26139	UAGUUAAAAGCCUACUUCU	1453	26139	UAGUUAAAAGCCUACUUCU	1453	26157	AGAAAGUAGCCUUAACUA	3104
26157	UUUUUCUUGGUUCUUGGGU	1454	26157	UUUUUCUUGGUUCUUGGGU	1454	26175	ACCAAGAAAAGCAAAAAAA	3105
26175	UAUUCUUGGUAGUCACAU	1455	26175	UAUUCUUGGUAGUCACAU	1455	26193	AGUGUGACUAGCAAGAAUA	3106
26193	UAGCCAUCCUUAUGGCCU	1456	26193	UAGCCAUCCUUAUGGCCU	1456	26211	AGCCGAGUAGGAUGGCCUA	3107
26211	UUCGAUUGUGGUACUG	1457	26211	UUCGAUUGUGGUACUG	1457	26229	CAGUAGGGCACACAAUCGAA	3108
26229	GCUGCAAUAUUGGUACGU	1458	26229	GCUGCAAUAUUGGUACGU	1458	26247	ACGUUJAACAAUUGGAGC	3109
26247	UGAGUUUAGGUAAAACCA	1459	26247	UGAGUUUAGGUAAAACCA	1459	26265	GUUGGUUUUACUAAACUCA	3110
26265	CGGUUUAGGUACUACUGCG	1460	26265	CGGUUUAGGUACUACUGCG	1460	26283	CGCGAGUAGACGUAAACCG	3111
26283	GUGUAAAAGGUACUACUC	1461	26283	GUGUAAAAGGUACUACUC	1461	26301	GAGGUUCAGUUCUJUAGAAG	3112
26301	CUUCUGAAAGGAGGUUCUGA	1462	26301	CUUCUGAAAGGAGGUUCUGA	1462	26319	UCAGGAACUCCUUCAGAAG	3113
26319	AUCUUCUGGUACUAAACGAA	1463	26319	AUCUUCUGGUACUAAACGAA	1463	26337	UCCGUUJAGACAGCAAGAU	3114
26337	ACUAACUUAUUAUUAU	1464	26337	ACUAACUUAUUAUUAU	1464	26355	AAUAAUAAUUAUUAU	3115

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26355	UCUGUUUUGGAACUUUAACA	1465	26355	UCUGUUUUGGAACUUUAACA	1465	26373	UGUAAAAGGUUCACAAAGA	3116
26373	AUUGCUUUAUCAGGCAAC	1466	26373	AUUGCUUUAUCAGGCAAC	1466	26391	GUUCGCCAUGUAAAGCAAU	3117
26391	AAACGGUACUAAUACCGUU	1467	26391	AAACGGUACUAAUACCGUU	1467	26409	ACGGGUAAUAGCUCGUUG	3118
26409	UGAGGAGGUAAAACACUC	1468	26409	UGAGGAGGUAAAACACUC	1468	26427	GAGGUUUUAGGUCCUCUCA	3119
26427	CCUGGAACAAUUGGAACUA	1469	26427	CCUGGAACAAUUGGAACUA	1469	26445	UAGGUUCCAUUAGGUCCAGG	3120
26445	AGUAAUAGGUUCCUAUC	1470	26445	AGUAAUAGGUUCCUAUC	1470	26463	GAUAGGAAACUUAUACU	3121
26463	CCUAGCCUGGAAUAGGUUA	1471	26463	CCUAGCCUGGAAUAGGUUA	1471	26481	UACAUAAUCCAGGUCAUAGG	3122
26481	ACUACAAUUGCCUAUCU	1472	26481	ACUACAAUUGCCUAUCU	1472	26499	AGAUUAGGCAAAUUGUAGU	3123
26499	UAUUCGGAACAGGGUUUUG	1473	26499	UAUUCGGAACAGGGUUUUG	1473	26517	CAAAACCUGUUCGGAUUA	3124
26517	GUACAUAAAAGGUUUGUU	1474	26517	GUACAUAAAAGGUUUGUU	1474	26535	AACAGGUUUUUAUAGUAC	3125
26535	UUUCCUCUGGUUUGUUGG	1475	26535	UUUCCUCUGGUUUGUUGG	1475	26553	CCACAAAGGCCAGAGGAAA	3126
26553	GGCAGGUACACUUGGUUGU	1476	26553	GGCAGGUACACUUGGUUGU	1476	26571	ACAAGGUUACUGGCC	3127
26571	UUUUGUUGGUUGGUUGGUUC	1477	26571	UUUUGUUGGUUGGUUGGUUC	1477	26589	GACAGGAGGAAGGAAAAAA	3128
26589	CUACAGAAUAAAUGGUG	1478	26589	CUACAGAAUAAAUGGUG	1478	26607	CACCCAUUUAUUCGUAG	3129
26607	GACUGGGGAUUGGCAUU	1479	26607	GACUGGGGGAUUGGCAUU	1479	26625	AAUCGCAAUCCGCCAGUC	3130
26625	UGCAAUUGGUUUGUUA	1480	26625	UGCAAUUGGUUUGUUA	1480	26643	UACAUAAUACAGGUUAUGCA	3131
26643	AGGCUUUGGUUGGUUAGC	1481	26643	AGGCUUUGGUUGGUUAGC	1481	26661	GCUAAGCCACAUCAAGCCU	3132
26661	CUACUUCGUUUGGUUUCU	1482	26661	CUACUUCGUUUGGUUUCU	1482	26679	GAAGGAAGGCAACGAAGUAG	3133
26679	CAGGCUGUUGGUUUCUACC	1483	26679	CAGGCUGUUGGUUUCUACC	1483	26697	GGUACGAGCAACAGCCUG	3134
26697	CGGCUCUAAUGGUUUCUUC	1484	26697	CGGCUCUAAUGGUUUCUUC	1484	26715	GAUAGGCCACAUUAGGCCGG	3135
26715	CAACCCAGAAACAAACAUU	1485	26715	CAACCCAGAAACAAACAUU	1485	26733	AAUGUUUUUCGUUGGUUGU	3136
26733	UCUUCUCAAUUGGCCUC	1486	26733	UCUUCUCAAUUGGCCUC	1486	26751	GAGGAGCACAUUAGGAAAGA	3137
26751	CGGGGGACAAUUGGACCC	1487	26751	CGGGGGACAAUUGGACCC	1487	26769	GGUACAAUJUGGUCCCCGG	3138
26769	CAGACCGCUCAUGGAAAGU	1488	26769	CAGACCGCUCAUGGAAAGU	1488	26787	ACUUUCCAUAGGGGUUCUG	3139
26787	UGAACUUGGUCAUUGGGCU	1489	26787	UGAACUUGGUCAUUGGGCU	1489	26805	AGCACCAUAGCAAGGUUCA	3140
26805	UGUGAUCAUUCUGGUUCAC	1490	26805	UGUGAUCAUUCUGGUUCAC	1490	26823	GUGACCCAGAAUGAUACACA	3141
26823	CUUGCGAACGGGGACAC	1491	26823	CUUGCGAACGGGGACAC	1491	26841	GUGJCCGGCCAUUCGCCAAG	3142
26841	CUCCCUAGGGCGUGUGAC	1492	26841	CUCCCUAGGGCGUGUGAC	1492	26859	GUACACGGGCCCUAGGGAG	3143
26859	CAUUAAGGACUCCAAA	1493	26859	CAUUAAGGACUCCAAA	1493	26877	UUUJGGAGGUCCUUAUAG	3144
26877	AGGAUCACUUGGCCUACA	1494	26877	AGGAUCACUUGGCCUACA	1494	26895	UGAUAGGCCACAGGUAGCUCU	3145
26895	AUCACGAAACGCUUUCUAU	1495	26895	AUCACGAAACGCUUUCUAU	1495	26913	AUAAGAAAAGGUUCUAGGU	3146
26913	UACAAAUUAGGGCGUCG	1496	26913	UACAAAUUAGGGCGUCG	1496	26931	CGACGUCCUACACGCC	3147
26931	CGAGCGUUGUAGGCACUGAU	1497	26931	CGAGCGUUGUAGGCACUGAU	1497	26949	AUCAGUGCCUACACGCC	3148
27039	UACAGGUUUCUGGUACAA	1503	27039	UACAGGUUUCUGGUACAA	1503	27057	UGUJGUACUUCAGGUACU	3149
27057	AGAUGUUUACIUGGUJA	1504	27057	AGAUGUUUACIUGGUJA	1504	27075	UCAACAAAGGUACAAUCU	3150
27075	ACUUCAGGUUACAAUAGC	1505	27075	ACUUCAGGUUACAAUAGC	1505	27093	GCJAUJGUUAACCUUGAAGU	3151
27093	CAGAGAUUUGAUJACAU	1506	27093	CAGAGAUUUGAUJACAU	1506	27111	AUGAAUAAUCAUAUCUUC	3152

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27111	UUAGAGGACUUUCAGGAU	1507	27111	UUAUUGGGACUUUCAGGAU	1507	27129	AUCCUGAAAGGUCCUCAUAA	3158
27129	UUGCUAUUUGGAUCUGA	1508	27129	UUGCUAUUUGGAUCUGA	1508	27147	UCAAGAUUCCAAAUGCAA	3159
27147	ACGUUAUAAAAGUICAAU	1509	27147	ACGUUAUAAAAGUICAAU	1509	27165	AUUGAACUUAAAAGCU	3160
27165	UAGUGAGACAAUJUJUAA	1510	27165	UAGUGAGACAAUJUJUAA	1510	27183	UAAAUAUAAAUGUCACUA	3161
27183	AGCCUCUAAACUAAAAGAA	1511	27183	AGCCUCUAAACUAAAAGAA	1511	27201	UUCUUCUJUAGUAGGCGU	3162
27201	AUUAUUCGGAGUJUAGUA	1512	27201	AUUAUUCGGAGUJUAGUA	1512	27219	UCAUCUAAUCUCGAAUAAU	3163
27219	AUGAAGAACCUUAGGAGU	1513	27219	AUGAAGAACCUUAGGAGU	1513	27237	AACUCUCAAGGUUCUCAU	3164
27237	UAGAUUUAUCCAUAAAAGCA	1514	27237	UAGAUUUAUCCAUAAAAGCA	1514	27255	UCGUUUUJUAGGUAAUCAA	3165
27255	AACAUGAAAUAUUAUCUCA	1515	27255	AACAUGAAAUAUUAUCUCA	1515	27273	AGAGAAUAAAUIUCAUGUU	3166
27273	UCCUGACAUUAGUJUGUAU	1516	27273	UCCUGACAUUAGUJUGUAU	1516	27291	AUACAAUCAUGUCAGGAA	3167
27291	UUUACACUUCUGGAGCUAU	1517	27291	UUUACACUUCUGGAGCUAU	1517	27309	AUAGCUCGCAGAUAAA	3168
27309	UAUACAUACUACAGGAGUG	1518	27309	UAUACAUACUACAGGAGUG	1518	27327	CACACUCUCUGAUAGUGAU	3169
27327	GUUAGAGGUACGACUGAC	1519	27327	GUUAGAGGUACGACUGAC	1519	27345	GUACAGUGGUACCUCCUAC	3170
27345	CUACUAAAAGAACCUUGCC	1520	27345	CUACUAAAAGAACCUUGCC	1520	27363	GGCCAAAGGUUCUUUUAGG	3171
27363	CCAUCAGGAUACGGAGG	1521	27363	CCAUCAGGAUACGGAGG	1521	27381	CCUCUGGUACGUUCUAGGG	3172
27381	GGCAAAUUCACCUUJUACC	1522	27381	GGCAAAUUCACCUUJUACC	1522	27399	GGGUAAAUGGUAAUUGCC	3173
27399	CGCUUUCUGCAGACAAUAA	1523	27399	CGCUUUCUGCAGACAAUAA	1523	27417	AUUIAUJUGCAGCAAGAGG	3174
27417	UUUGCACUAAUCUJGACUA	1524	27417	UUUGCACUAAUCUJGACUA	1524	27435	UAGUJCAAGUJUAGGCAA	3175
27435	AGCACACACUUGUUJUJG	1525	27435	AGCACACACUUGUUJUJG	1525	27453	CAAAGCAAAGJUGUGGCU	3176
27453	GUUUGUGGUACGGGUACUC	1526	27453	GUUUGUGGUACGGGUACUC	1526	27471	GAGUACCGGUACGACAAGC	3177
27471	CGACAUACCUAACUGCUGC	1527	27471	CGACAUACCUAACUGCUGC	1527	27489	GCACCGUGAUAGGUAGUGG	3178
27489	CGUGCAAGAUCAUGUUCAC	1528	27489	CGUGCAAGAUCAUGUUCAC	1528	27507	GUAGAAACUGAUJUGGACG	3179
27507	CCAAAACUUUCAUCAGAC	1529	27507	CCAAAACUUUCAUCAGAC	1529	27525	GUUCGUAGAAAAGUUUUGG	3180
27525	CAAGAGGGGUUCAACAG	1530	27525	CAAGAGGGGUUCAACAG	1530	27543	CUUUGGUACCUCCUUGG	3181
27543	GAAGCUCUACUUCGCCACUU	1531	27543	GAAGCUCUACUUCGCCACUU	1531	27561	AAAGUGGCCAGUAGGCU	3182
27561	UUUCUCAUUUGUJUGCUC	1532	27561	UUUCUCAUUUGUJUGCUC	1532	27578	GAGGAGGCAACAUAGAAA	3183
27578	CUAGUAUUUAAAUCUUU	1533	27579	CUAGUAUUUAAAUCUUU	1533	27597	AAAGUAAUAAAUAUCUAG	3184
27597	UGCUUACAOAUAAAAGAA	1534	27597	UGCUUACAOAUAAAAGAA	1534	27615	UUCUCUJUAGGUAGGCA	3185
27615	AGAGCAGAAUAGUAAUGAGC	1535	27615	AGAGCAGAAUAGUAAUGAGC	1535	27633	AGCUCAUJCACUUCUGCUU	3186
27633	UACUUAAAUGACUUCUA	1536	27633	UACUUAAAUGACUUCUA	1536	27651	UAGAAGLICAUJUAAAAGUGA	3187
27651	AUJUGUGGUJUJUJUGCUU	1537	27651	AUJUGUGGUJUJUJUGCUU	1537	27669	AAGGCCUAAAAGCACAAA	3188
27669	UUCUGCUAUUCCUJGUUU	1538	27669	UUCUGCUAUUCCUJGUUU	1538	27687	AAAAACAAGGAAUAGGAGA	3189
27687	AAAUAUUGCUUAAAUAU	1539	27687	AAAUAUUGCUUAAAUAU	1539	27705	AAAUAUAUUGCUUAAAUAU	3190
27705	UUUGGUJUJUCACUCGAAU	1540	27705	UUUGGUJUJUCACUCGAAU	1540	27723	AUUCUCGAGUAAAACAAA	3191
27723	UCCAGGAUCUAGAAACC	1541	27723	UCCAGGAUCUAGAAACC	1541	27741	GGUUCUJUJUAGUCCUGGA	3192
27741	CUUGUACCAAGGUCAAC	1542	27741	CUUGUACCAAGGUCAAC	1542	27759	GUUAGACUJUJUUGUACAAG	3193
27759	CGAACAUAAAACUUCUGAU	1543	27759	CGAACAUAAAACUUCUGAU	1543	27777	AUGAGAAGJUJUAGGUUCG	3194
27777	UUGUUUJUAGUJUJUUC	1544	27777	UUGUUUJUAGUJUJUUC	1544	27795	AAAAUACAAGGUAAAACAA	3195
27795	CUCUAAUGCAGUUGCAUAG	1545	27795	CUCUAAUGCAGUUGCAUAG	1545	27813	CAUAGGCAACUGCAUAG	3196
27813	GCACUGUAGUACAGGGCUG	1546	27813	GCACUGUAGUACAGGGCUG	1546	27831	CAGCCUGCUACUAGG	3197
27831	GGCAUCUAAAACCUCU	1547	27831	GGCAUCUAAAACCUCU	1547	27849	UGAGGUUUJUAGGACAC	3198
27849	AUGUGGUUJUAGGAGUUC	1548	27849	AUGUGGUUJUAGGAGUUC	1548	27867	CAAGGAUCUJUAGGACACAU	3199

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278867	GUAGGUACAACACUAGGG	1549	278867	GUAGGUACAACACUAGGG	1549	27885	CCCUAGGUUGGUACCUUAC	3200
278885	GGUAUAUCUUUAGCACUG	1550	278885	GGUAUAUCUUUAGCACUG	1550	27903	CAGUGCUUAAGUAUACC	3201
27903	GCUUUGGCUUUGGCCUUCAG	1551	27903	GCUUUGGCUUUGGCCUUCAG	1551	27921	CGAGGCACAAAGCCAAGC	3202
27921	GGAAAGGUUUUACCUUUC	1552	27921	GGAAAGGUUUUACCUUUC	1552	27939	GAAGAGGUAAAACCUUUC	3203
27939	CAUAGAUGGCCACACUAGG	1553	27939	CAUAGAUGGCCACACUAGG	1553	27957	CCAUAGUGGCCACAUAG	3204
27957	GUICAAACAUAGCACCUA	1554	27957	GUICAAACAUAGCACCUA	1554	27975	UAGGUGUGCAUGUJUGAAC	3205
27975	AUGGUACUACAUAGCUC	1555	27975	AUGGUACUACAUAGCUC	1555	27993	GACAGUAGUAGUACAUU	3206
27993	CAAGAUCCAGCUGGUUGGU	1556	27993	CAAGAUCCAGCUGGUUGGU	1556	28011	CACCAAGGUUGGUUGGUUG	3207
28011	GCGCUUUAUAGCUAGGUU	1557	28011	GCGCUUUAUAGCUAGGUU	1557	28029	AACACCUAGCUAAAGCGC	3208
28029	UGGUACCUUCAUGAAGGU	1558	28029	UGGUACCUUCAUGAAGGU	1558	28047	GACCUUCAUGAAGGUACCA	3209
28047	CACCAAACUGCUGCAUUA	1559	28047	CACCAAACUGCUGCAUUA	1559	28065	UAAAUGCAGCAGGUUGGU	3210
28065	AGAGACGUACUUGUUUU	1560	28065	AGAGACGUACUUGUUUU	1560	28083	AAACACAAAGUACGUCUCU	3211
28083	UAAAAUAAAAGGAACAAAU	1561	28083	UAAAAUAAAAGGAACAAAU	1561	28101	AAUJUJUJCQGUUUAUAAA	3212
28101	UAAAUGUCUGAUAAAUGGA	1562	28101	UAAAUGUCUGAUAAAUGGA	1562	28119	UCCAUUAUCAGACAUUUUA	3213
28119	ACCCAAUAAAACCAAGGU	1563	28119	ACCCAAUAAAACCAAGGU	1563	28137	ACGUUGGUUGGUAGGGGU	3214
28137	UAGUGGCCGCCGCCAUUACA	1564	28137	UAGUGGCCGCCGCCAUUACA	1564	28155	UGGUAAUGGCCGGGGCACUA	3215
28155	AUUUGGUUGGCCACAGAU	1565	28155	AUUUGGUUGGCCACAGAU	1565	28173	AUCJUGUGGUUGGCCACAAAU	3216
28173	UUCAACUGACAAUACCAAG	1566	28173	UUCAACUGACAAUACCAAG	1566	28191	CUGGUUAUJUGUCAGUJGAA	3217
28191	GAAUGGGAGCAGCAUAGG	1567	28191	GAAUGGGAGCAGCAUAGG	1567	28209	CCCAUJUGGUUCUCCAUUC	3218
28209	GGCAAGGCCAAAAGCGGC	1568	28209	GGCAAGGCCAAAAGCGGC	1568	28227	GCGCUGUUUUGGCCUUGGC	3219
28227	CCGACCCCAGGUUJACCC	1569	28227	CCGACCCCAGGUUJACCC	1569	28245	GGGUAAACCUUJGGGUUGGG	3220
28245	CAUAAAUCUGCCGUUJGG	1570	28245	CAUAAAUCUGCCGUUJGG	1570	28263	CCAAAGACGGCAGUAAAUG	3221
28263	GUUCACAGCUCUCACUCAG	1571	28263	GUUCACAGCUCUCACUCAG	1571	28281	CUGGAGUGAGCUGUGUGAAC	3222
28281	CGAUGGCAAGGAGGAACUU	1572	28281	CGAUGGCAAGGAGGAACUU	1572	28299	AAGUUCUCCUUGGUCCAUUC	3223
28299	UAGAUUUCCCUCGGGCAG	1573	28299	UAGAUUUCCCUCGGGCAG	1573	28317	CUGGCCUCGGGAAUUCUA	3224
28317	GGGCGUUCUCAUACACCC	1574	28317	GGGCGUUCUCAUACACCC	1574	28335	GGGUUGUAGUUGAACGCC	3225
28335	CAAUAGUGGUCCAGAUGAC	1575	28335	CAAUAGUGGUCCAGAUGAC	1575	28353	GUCAUCUGGACACCUAUUG	3226
28353	CAAAUUUGGUACUACCGA	1576	28353	CAAAUUUGGUACUACCGA	1576	28371	UCGGUAGUAGCAGGUUGG	3227
28371	AAGAGGUACCCGAGGAGUU	1577	28371	AAGAGGUACCCGAGGAGUU	1577	28389	AACUCUCUGGGGUAGCCUCU	3228
28389	UCGUGGUUGGUAGGCCAAA	1578	28389	UCGUGGUUGGUAGGCCAAA	1578	28407	UJUJGCGGUACACCCACGA	3229
28407	AUGAAAAGGAGCUCAGCCCC	1579	28407	AUGAAAAGGAGCUCAGCCCC	1579	28425	GGGGCUGAGGCUCUUCUAU	3230
28425	CAGAUGGUACUUCUUAUC	1580	28425	CAGAUGGUACUUCUUAUC	1580	28443	GUAAUAGAAGUACCAUCUG	3231
28443	CGUAGGAUCUUGGCCAGAA	1581	28443	CGUAGGAUCUUGGCCAGAA	1581	28461	UUCJUGGGCCAGUGGUAGGG	3232
28461	AGCUUUCACUUCUACGGC	1582	28461	AGCUUUCACUUCUACGGC	1582	28479	GCCGUAGGGGUAGGUAGGG	3233
28479	CGCUAACAAAGGAAGGCAUC	1583	28479	CGCUAACAAAGGAAGGCAUC	1583	28497	GAUGCCUCUJGUAGGUAGGG	3234
28497	CGUAUGGGUUGCAACUGAG	1584	28497	CGUAUGGGUUGCAACUGAG	1584	28515	CUCAGUUGGCAACCCAUACG	3235
28515	GGGAGGCCUUGAAUACCCC	1585	28515	GGGAGGCCUUGAAUACCCC	1585	28533	GGGUUGUUAUAGGGGUCC	3236
28533	CAAAGACCCACAUUGGCC	1586	28533	CAAAGACCCACAUUGGCC	1586	28551	GGUGCCAAUGGGGUJJUG	3237
28551	CGGCAAUCUCAUAAACAU	1587	28551	CGGCAAUCUCAUAAACAU	1587	28569	AUJGUUAUJAGGUUGGG	3238
28569	UGCUGGCCACCGUGGUACAA	1588	28569	UGCUGGCCACCGUGGUACAA	1588	28587	UJGUAGGCACGGGUCCAGCA	3239
28587	ACUUCUCUAGGAACAAAC	1589	28587	ACUUCUCUAGGAACAAAC	1589	28605	UGGUUGUUCUUGAGGAAGU	3240
28605	AUUGCCAAAAGGCCUUCUAC	1590	28605	AUUGCCAAAAGGCCUUCUAC	1590	28623	GUAGAAGGCCUUIGGCAAU	3241

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28623	CGCAGAGGGAAAGCAGGGC	1591	28623	CGCAGAGGGAAAGCAGGGC	1591	28641	GCCUCUGCUUCCCCUCUGGG	3242
28641	GGGAGCUCAAGGCCUCUUCU	1592	28641	GGGAGCUCAAGGCCUCUUCU	1592	28659	AGAAGGGCUUAGCUGGCC	3243
28659	UCGGCUCCUCUCAUCGUAGU	1593	28659	UCGGCUCCUCUCAUCGUAGU	1593	28677	ACUACGUGAUAGGGAGCGA	3244
28677	UGGGGGUAUUCGUAGAAAUAU	1594	28677	UGGGGGUAUUCGUAGAAAUAU	1594	28695	AUUUCIUGUAUACCGCGA	3245
28695	UUCAACUCUCCUGGCAGAGU	1595	28695	UUCAACUCUCCUGGCAGAGU	1595	28713	ACUUCUGCCAGGAGUIGAA	3246
28713	UAGGGGAAUUCUCCUGGCC	1596	28713	UAGGGGAAUUCUCCUGGCC	1596	28731	AGCAGGGAAUUCUCCUA	3247
28731	UCGAAUUGGUAGCGGAAGU	1597	28731	UCGAAUUGGUAGCGGAAGU	1597	28749	ACCCGCUAGCCAUUCGA	3248
28749	UGGUGAAACUGGCCUGGCC	1598	28749	UGGUGAAACUGGCCUGGCC	1598	28767	CGCGAGGGAAUUCUCCAA	3249
28767	GUCAUUUGCUGCUAGACAGA	1599	28767	GUCAUUUGCUGCUAGACAGA	1599	28785	UCUUGCUUAGCAGCAAUAGC	3250
28785	AUUGAACCCAGCUUAGAGC	1600	28785	AUUGAACCCAGCUUAGAGC	1600	28803	GCUUCUAGCUGGUUCAAU	3251
28803	CAAAGUUUUCGUUAGGGC	1601	28803	CAAAGUUUUCGUUAGGGC	1601	28821	GCUUUUACCGAAAUCUUG	3252
28821	CACAACAAACAACAGGCCAA	1602	28821	CACAACAAACAACAGGCCAA	1602	28839	UUGGCCUUGGUUGGUUGUG	3253
28839	AACUGUCACUAGAAAUCU	1603	28839	AACUGUCACUAGAAAUCU	1603	28857	AGAUUUCUAGUGACAGU	3254
28857	UGCGUGCGGGCAUCUAAA	1604	28857	UGCGUGCGGGCAUCUAAA	1604	28875	UUUAGAUGCCUCAGCAGCA	3255
28875	AAAGCCUCGCCAAAACGU	1605	28875	AAAGCCUCGCCAAAACGU	1605	28893	ACGUUUUUGGGAGGCCUUU	3256
28893	UACUGCCACAAAACGUAC	1606	28893	UACUGCCACAAAACGUAC	1606	28911	GUACUAGUUGGGAGCGAGUA	3257
28911	CAACGUACUCAAGCAUUU	1607	28911	CAACGUACUCAAGCAUUU	1607	28929	AAAUGCUUUGAGGACGUUG	3258
28929	UGGGAGACGGGUCCAGAA	1608	28929	UGGGAGACGGGUCCAGAA	1608	28947	UUCUGGACCACGUCCCA	3259
28947	ACAAACCCAAGGAAAUUC	1609	28947	ACAAACCCAAGGAAAUUC	1609	28965	GAUUUUCUUGGGUUUUGU	3260
28965	CGGGGACCAAGACCUAAC	1610	28965	CGGGGACCAAGACCUAAC	1610	28983	GAUAGGUCCUGGUCCCCG	3261
28983	CAGACAAGGAACGUUJAC	1611	28983	CAGACAAGGAACGUUJAC	1611	29001	GUAAUCAGUUCUUGUCUG	3262
29001	CAAACAUUGGCCGCAAAU	1612	29001	CAAACAUUGGCCGCAAAU	1612	29019	AAUUIUGGGCCAAUGUUUG	3263
29019	UGCCACAUUUGGUCCUAGU	1613	29019	UGCCACAUUUGGUCCUAGU	1613	29037	ACUUGGAGAAUUGUGGCA	3264
29037	UGCCUCUGGUCCUUGGGA	1614	29037	UGCCUCUGGUCCUUGGGA	1614	29055	CUUAGAAGUGCAGAGGCA	3265
29055	AUGGUACACCCAUUGGCAUG	1615	29055	AUGGUACACCCAUUGGCAUG	1615	29073	CAUGCCAAUUGGUAGCACAU	3266
29073	GGAAGGUACACCCUUGGGA	1616	29073	GGAAGGUACACCCUUGGGA	1616	29091	UCCGGAAAGGUAGCACUCC	3267
29091	AACAUGGCGACUUAUCAU	1617	29091	AACAUGGCGACUUAUCAU	1617	29109	AUGAAUAGGUAGCCAUUU	3268
29109	UGGAGCCAUUAAAUGGAU	1618	29109	UGGAGCCAUUAAAUGGAU	1618	29127	AUCCAUUUAUAGGUCCAU	3269
29127	UGACAAAGGUUCCACAAUUC	1619	29127	UGACAAAGGUUCCACAAUUC	1619	29145	GAUUUGGUUCCAUUUGUCA	3270
29145	CAAAGACAAACGUUACUG	1620	29145	CAAAGACAAACGUUACUG	1620	29163	CAGLAIUGACGUUUCUUG	3271
29163	GCUGAACAGCACAUUGAC	1621	29163	GCUGAACAGCACAUUGAC	1621	29181	GUCAAAUGGUUUCUAGC	3272
29181	CGCAUACAAAACAUCCCC	1622	29181	CGCAUACAAAACAUCCCC	1622	29199	UGGGAAUUGGUUUGUAUGGG	3273
29199	ACCAACAGGCCUAAAAG	1623	29199	ACCAACAGGCCUAAAAG	1623	29217	CUUCUUUUGUCUUGGUUGU	3274
29217	GGACAAAAAGAAAAAGACU	1624	29217	GGACAAAAAGAAAAAGACU	1624	29235	AGUCUUUUUUCUUGGUUC	3275
29235	UGAUGAACGUUCCUJUG	1625	29235	UGAUGAACGUUCCUJUG	1625	29253	CAAAGGGCUAGGUUCAUCA	3276
29253	GCGCAGAGAACAAAGAAG	1626	29253	GCGCAGAGAACAAAGAAG	1626	29271	CUUCUUUUUGUCUUGGGCC	3277
29271	GCAGCCCCACUGUGACUUU	1627	29271	GCAGCCCCACUGUGACUUU	1627	29289	AAGAGUACAGUGGGUGCC	3278
29289	UCUUCUCUGGGCUGACAU	1628	29289	UCUUCUCUGGGCUGACAU	1628	29307	CAUGUICAGCCCCAGGAAGA	3279
29307	GGAUCAUUCUCCAGACAA	1629	29307	GGAUCAUUCUCCAGACAA	1629	29325	UUGLICUGGAGAAUCAUCC	3280
29325	ACUUCAAAAUUCCAUGAGU	1630	29325	ACUUCAAAAUUCCAUGAGU	1630	29343	ACUCAUGGAAUJJUGAAGU	3281
29343	UGGAGCUUUCUGCUAUCA	1631	29343	UGGAGCUUUCUGCUAUCA	1631	29361	UGAAUCAGCAGAAGCUCCA	3282
29361	AACUCAGGCAAAAACACUC	1632	29361	AACUCAGGCAAAAACACUC	1632	29379	GAGGUUUUAGGCCUGAGUU	3283

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29379	CAUGAUGACCCACACAAGGC	1633	29379	CAUGAUGACCCACACAAGGC	1633	29397	GCCUJUGUGGGGUCAUCAG	3284
29397	CAGAUUGGGCUAUGUAACG	1634	29397	CAGAUUGGGCUAUGUAACG	1634	29415	CGUUUACAUAGCCCCAUCUG	3285
29415	GUUUUUCGCCAUUCGUUUA	1635	29415	GUUUUUCGCCAUUCGUUUA	1635	29433	UAAAACGGAAUUGCGAAAAAC	3286
29433	ACGAUACAUAGUCUACUCU	1636	29433	ACGAUACAUAGUCUACUCU	1636	29451	AGAGUAGACUAGUUAUCGU	3287
29451	UGUUGCCAGAAUGAAUUCUC	1637	29451	UGUUGCCAGAAUGAAUUCUC	1637	29469	GAGAAUUCAUUCUGCACAA	3288
29469	CGUAACUAACAGGCACAAAG	1638	29469	CGUAACUAACAGGCACAAAG	1638	29487	CUUJUGUGGUAGUUAUCG	3289
29487	GUAGGGUUUAGUUAAUCUUUA	1639	29487	GUAGGGUUUAGUUAAUCUUUA	1639	29505	UAAAAGGUAAACUAAACCUCAC	3290
29505	AUCUCACAUAGCAAUCUU	1640	29505	AUCUCACAUAGCAAUCUU	1640	29523	AAGAUUGCAGUGAGAUUJ	3291
29523	UAAAUCAAUGUGUAACAUU	1641	29523	UAAAUCAAUGUGUAACAUU	1641	29541	AAUGGUUACACAUUGAUUAA	3292
29541	UAGGGAGGGACUUGAAAGAG	1642	29541	UAGGGAGGGACUUGAAAGAG	1642	29559	CUCUUUCAAGGUCCCCUUA	3293
29559	GCCCACCAAUUUUCAUCGA	1643	29559	GCCCACCAAUUUUCAUCGA	1643	29577	UCGAUGAAAAAUUGGUUGGCC	3294
29577	AGGCCAACGGGGGUACGAU	1644	29577	AGGCCAACGGGGGUACGAU	1644	29595	AUCGUACUCCGGGUUGGCCU	3295
29595	UCGAGGGGUACAGUGAAUAA	1645	29595	UCGAGGGGUACAGUGAAUAA	1645	29613	UUAUUUCACUGUACCCUCGA	3296
29613	AUGCUJAGGGAGAGCUCCU	1646	29613	AUGCUJAGGGAGAGCUCCU	1646	29631	AGGAGCAGCUUCUCCUAGAU	3297
29631	UAUAUGGAAGAGGCCCUAAU	1647	29631	UAUAUGGAAGAGGCCCUAAU	1647	29649	AUJJAGGGGUCCUCAUAUA	3298
29649	UGUGUAAAUAUUAUJJAG	1648	29649	UGUGUAAAUAUUAUJJAG	1648	29667	CUAAAUAUUAUJJUACACA	3299
29667	GUAGUGGUACUCCCCAUGUG	1649	29667	GUAGUGGUACUCCCCAUGUG	1649	29685	CACAUAGGGGUAGGCACUAC	3300
29685	GAUUUUAAAUGGUUCUAG	1650	29685	GAUUUUAAAUGGUUCUAG	1650	29703	CUAAGGAAGGUAAUAAAUC	3301
29703	GGAGAAUGACAAAAAA	1651	29703	GGAGAAUGACAAAAAA	1651	29721	UUUUUUUUUGGUCAUUCUCC	3302

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence, for the lower sequence is optionally complementary to a portion of the target sequence. The overhang can comprise the general structure B, BNN, NN, BNsN, or NsN, where B stands for any terminal cap moiety, N stands for any nucleotide (e.g., thymidine) and s stands for phosphorothioate or other internucleotide linkage as described herein (e.g. internucleotide linkage having Formula I). The upper sequence is also referred to as the sense strand, whereas the lower sequence is also referred to as the antisense strand. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII or any combination thereof (see for example chemical modifications as shown in Table V herein).

Table III: SARS synthetic siNA and Target Sequences

Target Pos	Target	SeqID	RPI#	Aliases	Sequence	SeqID
1655	UGAAUGAAGGGUIGGCCAUCAUU	3303	SARS:1657U21 siRNA sense		AAUGGAGGGUIGGCCAUCAATT	3311
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA sense		UGCAUCUCCACAGGAGUGTT	3312
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2383U21 siRNA sense		CAAAGCAAGGGACUUUACCTT	3313
2598	CUGUGUAAAUGGCCCUAUGCUCU	3306	SARS:2600U21 siRNA sense		GUGUAAAUGGCCCUAUGCUCUTT	3314
26572	UUUGUGCUUUGCUGCUUACAG	3307	SARS:2657U21 siRNA sense		UGUGCUUUGCUGCUUACACTT	3315
26790	ACUUGUCAUUUGGUGUGAUCA	3308	SARS:2679U21 siRNA sense		UUGUCAUUUGGUGUGAUATT	3316
28786	UUGAACCGCUUUGAGGAAAGU	3309	SARS:2878U21 siRNA sense		GAACACGCUUUGAGGAAATT	3317
26529	GCUUUGUUUUUCUCUGGCCUUUGU	3310	SARS:2653U21 siRNA sense		UUGUUIUUCUCUGGCCUUUTT	3318
1655	UGAAUGAAGGGUIGGCCAUCAUU	3303	SARS:1675U21 siRNA (1657C) antisense		UGAUGGCAACCUUUCAUUTT	3319
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:2401U21 siRNA (2383C) antisense		CACUCCUGUGGGAGAUGCAATT	3320
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2618U21 siRNA (2600C) antisense		GGUAAGUCCCUUUGGUUGTT	3321
2598	CUGUGUAAAUGGCCCUAUGCUCU	3306	SARS:2659U21 siRNA (2657C) antisense		AGCAUGAGGCCAUUACACTT	3322
26572	UUUGUGCUUUGCUGCUUACAG	3307	SARS:2687U21 siRNA (2679C) antisense		GUAGACAGGCAGGAAGCACATT	3323
26790	ACUUGUCAUUUGGUGUGAUCA	3308	SARS:2886U21 siRNA (2878C) antisense		AUCACAGCACCAAUGACAATT	3324
28786	UUGAACCGCUUUGAGGAAAGU	3309	SARS:2654U21 siRNA (26531C) antisense		UUUGUCUCUAAUGGGUUUCCTT	3325
26529	GCUUUGUUUUUCUCUGGCCUUUGU	3310	SARS:2383U21 siRNA (26531C) antisense		AAGAGCCAGAGGGAAAAACAATT	3326
1655	UGAAUGAAGGGUIGGCCAUCAUU	3303	SARS:1657U21 siRNA stab04 sense		BAAUGGAAGGGUIGGCCAUATT B	3327
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1666U21 siRNA stab04 sense		BuuGCAUCUCCACAGGAGUGTT B	3328
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2383U21 siRNA stab04 sense		B CAAAGCAAGGGACUUUACCTT B	3329
2598	CUGUGUAAAUGGCCCUAUGCUCU	3306	SARS:2600U21 siRNA stab04 sense		B GuGUAAGGCUUAGGCUUUTT B	3330
26572	UUGUGCUUUGCUGCUUACAG	3307	SARS:2657U21 siRNA stab04 sense		B uGuGCUUAGGCUUAGCUUACTT B	3331
26790	ACUUGUCAUUUGGUGUGAUCA	3308	SARS:2679U21 siRNA stab04 sense		B uuGCAUuGGCUUAGGCUUATT B	3332
28786	UUGAACCGCUUUGAGGAAAGU	3309	SARS:2878U21 siRNA stab04 sense		B GAAccAGCUUAGAGGAAATT B	3333
26529	GCUUUGUUUUUCUCUGGCCUUUGU	3310	SARS:2653U21 siRNA stab04 sense		B uuGuuUccUUCUUGGCUUUTT B	3334
1655	UGAAUGAAGGGUIGGCCAUCAUU	3303	SARS:1675U21 siRNA (1657C) stab05 antisense		uGAUGGCAAccUUCUUGGCUUUTT	3335
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1184U21 siRNA (1166C) stab05 antisense		cACUUCUUGGAGAUGGAATST	3336

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2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2401L21 siRNA (2383C) slab05 antisense	GGUAAAAGUCCCUUGcuuGTst	3337
2598	CUGUGUAAAUGGCCUCAUGCUUCU	3306	SARS:2681L21 siRNA (2600C) slab05 antisense	AGcAuGAGGCCAUuAcActst	3338
26572	UUUGUGCUUJGGUGGUCAUCAG	3307	SARS:26592L21 siRNA (26574C) slab05 antisense	GUAGACAGCAGCAAGGCACAtst	3339
26790	ACUUGGUCAUUGGGUGGUCAUCA	3308	SARS:26810L21 siRNA (26792C) slab05 antisense	AucACAGCACCAGAACAAUAcAtst	3340
28786	UUGAACCCAGCUUGAGGCAAAGU	3309	SARS:28806L21 siRNA (28788C) slab05 antisense	uuuGuCucuAAGGcuGGGuicTsT	3341
26529	GCUUGUUUUCUUCGGCUUCUUGU	3310	SARS:26549L21 siRNA (26531C) slab05 antisense	AAGAGGcAGAGGAAAACAAAtst	3342
1655	UGAAUGAAGAGGGUGGCCAUCAUU	3303	SARS:1657U21 siRNA slab07 sense	BAAuGAAGAGGGGuuGccAuCATtB	3343
1164	UGUGGCAUCUCCACAGGGAGUGUA	3304	SARS:1166U21 siRNA slab07 sense	BuuggcAucuccAcAGGGAGuGTTB	3344
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2383U21 siRNA slab07 sense	BcAAAGGAAGGGACuuuAcCttB	3345
2598	CUGUGUAAAUGGCCUCAUGCUUCU	3306	SARS:2600U21 siRNA slab07 sense	BGuGuaAAuUGGcucuAuGcUttB	3346
26572	UUUGUGCUUJGGUGGUCAUCAG	3307	SARS:26574U21 siRNA slab07 sense	BuGuGcuuGcuGGuGcUAcTTB	3347
26790	ACUUGGUCAUUGGGUGGUCAUCA	3308	SARS:26792U21 siRNA slab07 sense	BuGuGcuuGGGuGGuGauTTB	3348
28786	UUGAACCCAGCUUGAGGCAAAGU	3309	SARS:28788U21 siRNA slab07 sense	BGAACcAGGuuGAGAGGAAATTB	3349
26529	GCUUGUUUUCUUCGGCUUCUUGU	3310	SARS:26531U21 siRNA slab07 sense	BuGuuGuuuccuGGGuicuUTTB	3350
1655	UGAAUGAAGAGGGUUGGCCAUUU	3303	SARS:1675L21 siRNA (1657C) slab11 antisense	uGAUGGGcAACCUuCuuAuWTst	3351
1164	UGUUGCAUCUCCACAGGGAGUGUA	3304	SARS:1184L21 siRNA (1166C) slab11 antisense	cAcucuGuGGGAGAuGcAAtst	3352
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2401L21 siRNA (2383C) slab11 antisense	GGUAAAAGUCCCUUGcuuGTst	3353
2598	CUGUGUAAAUGGCCUCAUGCUUCU	3306	SARS:2618L21 siRNA (2600C) slab11 antisense	AGcAuGAGGCCAUuAcActst	3354
26572	UUUGUGCUUJGGUGGUCAUCAG	3307	SARS:26592L21 siRNA (26574C) slab11 antisense	GuAGACAGCAGCAAGGCACAtst	3355
26790	ACUUGGUCAUUGGGUGGUCAUCA	3308	SARS:26810L21 siRNA (26792C) slab11 antisense	AucACAGCACCAGAACAAUAcAtst	3356
28786	UUGAACCCAGCUUGAGGCAAAGU	3309	SARS:28806L21 siRNA (28788C) slab11 antisense	uuuGuCucuAAGGGuGGuicTsT	3357
26529	GUUGGUUUUCUUCGGCUUCUUGU	3310	SARS:26549L21 siRNA (26531C) slab11 antisense	AAGAGcAGAGGGAAAACAAAtst	3358
1655	UGAAUGAAGAGGUUGGCCAUUU	3303	SARS:1657U21 siRNA slab08 sense	AAuGAAGAGGGGuuGccAuCAtst	3359
1164	UGUUGCAUCUCCAGGGAGUGUA	3304	SARS:1166U21 siRNA slab08 sense	uuGcAuCucuAGAGGAGuGtst	3360
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2383U21 siRNA slab08 sense	CAAAGcAAAGGGACuuuAccTsT	3361
2598	CUGUGUAAAUGGCCUCAUGCUUCU	3306	SARS:2600U21 siRNA slab08 sense	GuGuAAAuGGccuAuGcUtsT	3362

(400/110_US)

26572	UUUGGUCCUUGCCUGCUACAG	3307	SARS:26574U21 siRNA stab08 sense	uGuGcuuGcuGcuGcuUAcTsT	3363
26790	ACUUGGUCAUUGGGUGCUGAUCA	3308	SARS:26792U21 siRNA stab08 sense	uuGuaAuuGGGUcuGGuGAUTsT	3364
28786	UUGAACCGCUUAGAGGCAAAGU	3309	SARS:28788U21 siRNA stab08 sense	GAACAGcuuGAGAGCAAATsT	3365
26529	GCUUUUUCUCUGGCCUUGU	3310	SARS:26531U21 siRNA stab08 sense	uuGuuuuccuGGuGcuuUTsT	3366
1655	UGAAUGAAGAGGGUIGCCAUUU	3303	SARS:1675L21 siRNA (1657C) stab08 antisense	uGAUGGcAACccuucAuUTsT	3367
1164	UGUUGCAUCUCCACAGGUGUA	3304	SARS:1184L21 siRNA (1166C) stab08 antisense	cACUcGUGGAGAGGcAAATsT	3368
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2401L21 siRNA (2383C) stab08 antisense	GGuAAA GucccuuGcuuUGTsT	3369
2598	CUGUGUAAAUGGCCCUAUGCUCU	3306	SARS:2618L21 siRNA (2600C) stab08 antisense	AGcAUAGGGcAAuuaAcACTsT	3370
26572	UUUGGUCCUUGCCUGCUACAG	3307	SARS:26592L21 siRNA (26574C) stab08 antisense	GuAGAcAGcAGcAGGcAcATsT	3371
26790	ACUUGGUCAUUGGGUGCUGAUCA	3308	SARS:26810L21 siRNA (26792C) stab08 antisense	AucAcAGcAccAAuGcAAATsT	3372
28786	UUGAACCGCUUAGAGGCAAAGU	3309	SARS:28806L21 siRNA (28788C) stab08 antisense	uuuGcuuAAGGUcGGuuctsT	3373
26529	GCUUUUUCUCUGGCCUUGU	3310	SARS:26549L21 siRNA (26531C) stab08 antisense	AAGAGGcAGAGGAAAACAAATsT	3374

Uppercase = ribonucleotide

u,c = 2'-deoxy-2'-fluoro U, C

A = 2'-O-methyl Adenosine

G = 2'-O-methyl Guanosine

T = thymidine

B = inverted deoxy abasic

s = phosphorothioate linkage

A = deoxy Adenosine

G = deoxy Guanosine

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16"	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		Usually AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end -		Usually AS

CAP = any terminal cap, see for example Figure 10.

All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues

All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.

S = sense strand AS = antisense strand

Table V**A. 2.5 µmol Synthesis Cycle ABI 394 Instrument**

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 µL	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 µL	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 µL	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	845 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 µmol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 µL	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 µL	45 sec	233 min	465 sec
Acetic Anhydride	655	124 µL	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 µL	5 sec	5 sec	5 sec
TCA	700	732 µL	10 sec	10 sec	10 sec
Iodine	20.6	244 µL	15 sec	15 sec	15 sec
Beaucage	7.7	232 µL	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 µmol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O- methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O- methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 µL	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 µL	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 µL	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 µL	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 µL	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 µL	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 µL	NA	NA	NA

5 • Wait time does not include contact time during delivery.

• Tandem synthesis utilizes double coupling of linker molecule

CLAIMS

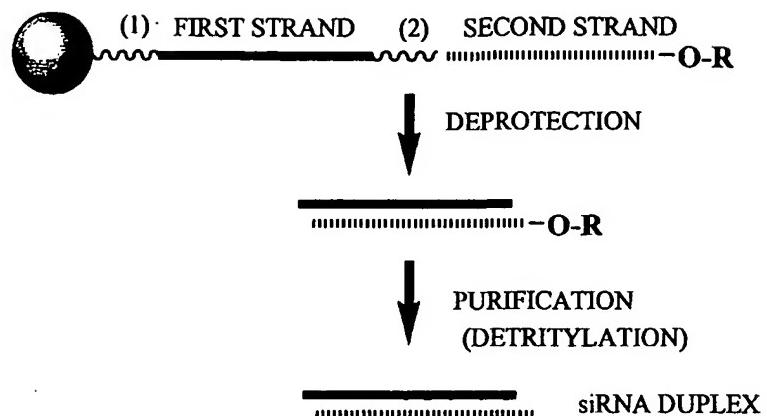
What we claim is:

1. A chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a severe acute respiratory syndrome (SARS) virus RNA via RNA interference, wherein:
 - a. each strand of said siNA molecule is about 19 to about 23 nucleotides in length;
 - b. one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said SARS virus RNA for the siNA molecule to direct cleavage of the SARS virus RNA via RNA interference; and
 - c. said siNA molecule does not require the presence of nucleotides having a 2'-hydroxy group for mediating RNA interference.
2. The siNA molecule of claim 1, wherein said siNA molecule comprises no ribonucleotides.
- 15 3. The siNA molecule of claim 1, wherein said siNA molecule comprises ribonucleotides.
4. The siNA molecule of claim 1, wherein one strand of said double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein a second strand of 20 said double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of said SARS virus RNA.
5. The siNA molecule of claim 4, wherein each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand.
- 25 6. The siNA molecule of claim 1, wherein said siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein said siNA further comprises a sense region, wherein said sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of said SARS virus gene or a portion thereof.

7. The siNA molecule of claim 6, wherein said antisense region and said sense region comprises about 19 to about 23 nucleotides, and wherein said antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region.
- 5 8. The siNA molecule of claim 1, wherein said siNA molecule comprises a sense region and an antisense region, and wherein said antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS virus gene, or a portion thereof, and said sense region comprises a nucleotide sequence that is complementary to said antisense region.
- 10 9. The siNA molecule of claim 6, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region of said siNA molecule.
10. The siNA molecule of claim 6, wherein said sense region is connected to the antisense region via a linker molecule.
- 15 11. The siNA molecule of claim 10, wherein said linker molecule is a polynucleotide linker.
12. The siNA molecule of claim 10, wherein said linker molecule is a non-nucleotide linker.
13. The siNA molecule of claim 6, wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides.
- 20 14. The siNA molecule of claim 6, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides.
15. The siNA molecule of claim 6, wherein pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
- 25 16. The siNA molecule of claim 9, wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment comprising said sense region.
17. The siNA molecule of claim 16, wherein said terminal cap moiety is an inverted deoxy abasic moiety.
- 30 18. The siNA molecule of claim 6, wherein pyrimidine nucleotides of said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides

19. The siNA molecule of claim 6, wherein purine nucleotides of said antisense region are 2'-O-methyl purine nucleotides.
20. 20. The siNA molecule of claim 6, wherein purine nucleotides present in said antisense region comprise 2'-deoxy- purine nucleotides.
- 5 21. The siNA molecule of claim 18, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.
22. The siNA molecule of claim 6, wherein said antisense region comprises a glyceryl modification at the 3' end of said antisense region.
- 10 23. The siNA molecule of claim 9, wherein each of the two fragments of said siNA molecule comprise 21 nucleotides.
24. The siNA molecule of claim 23, wherein about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule.
- 15 25. The siNA molecule of claim 24, wherein each of the two 3' terminal nucleotides of each fragment of the siNA molecule are 2'-deoxy-pyrimidines.
26. The siNA molecule of claim 25, wherein said 2'-deoxy-pyrimidine is 2'-deoxy-thymidine.
- 20 27. The siNA molecule of claim 23, wherein all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule.
28. The siNA molecule of claim 23, wherein about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
- 25 29. The siNA molecule of claim 23, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
30. The siNA molecule of claim 9, wherein the 5'-end of the fragment comprising said antisense region optionally includes a phosphate group.

31. A pharmaceutical composition comprising the siNA molecule of claim 1 in an acceptable carrier or diluent.

Figure 1

= SOLID SUPPORT

R = TERMINAL PROTECTING GROUP

FOR EXAMPLE:

-DIMETHOXYSYTRITYL (DMT)

(1)

~~~~~ = CLEAVABLE LINKER  
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR

INVERTED DEOXYABASIC SUCCINATE)

(2)

~~~~~ = CLEAVABLE LINKER

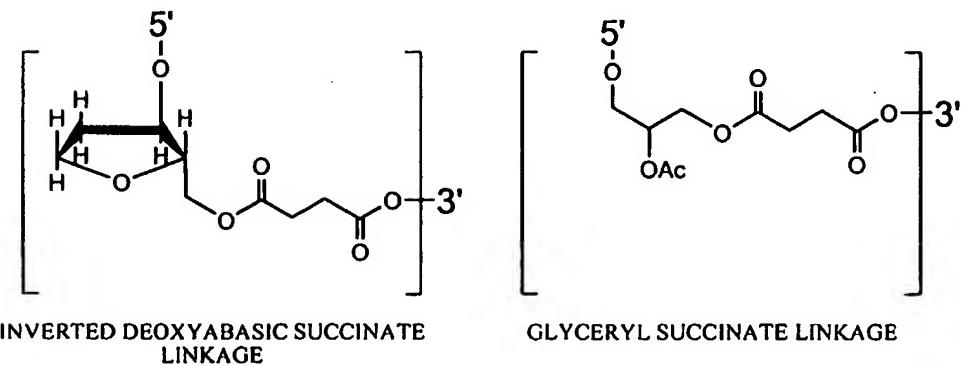
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
INVERTED DEOXYABASIC SUCCINATE)

Figure 2

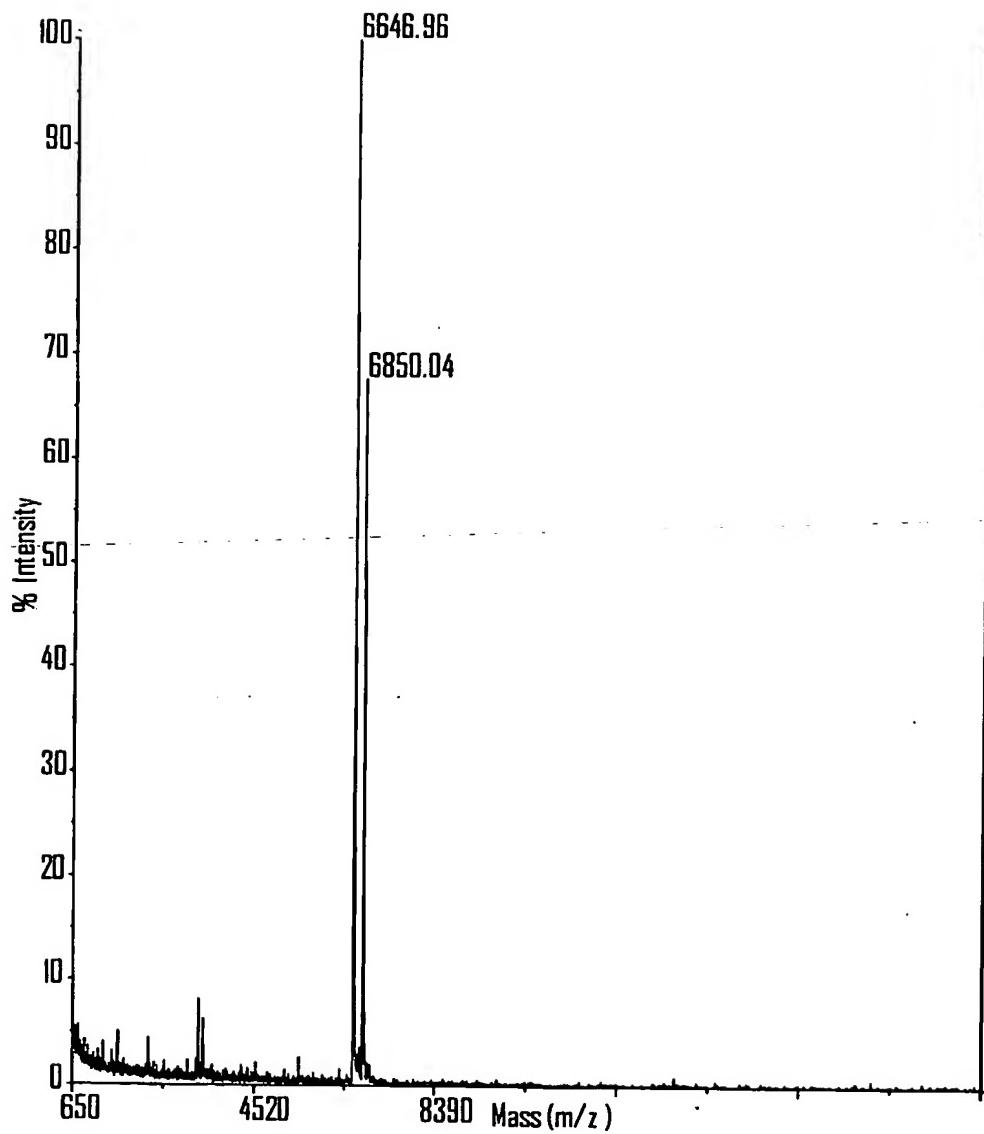


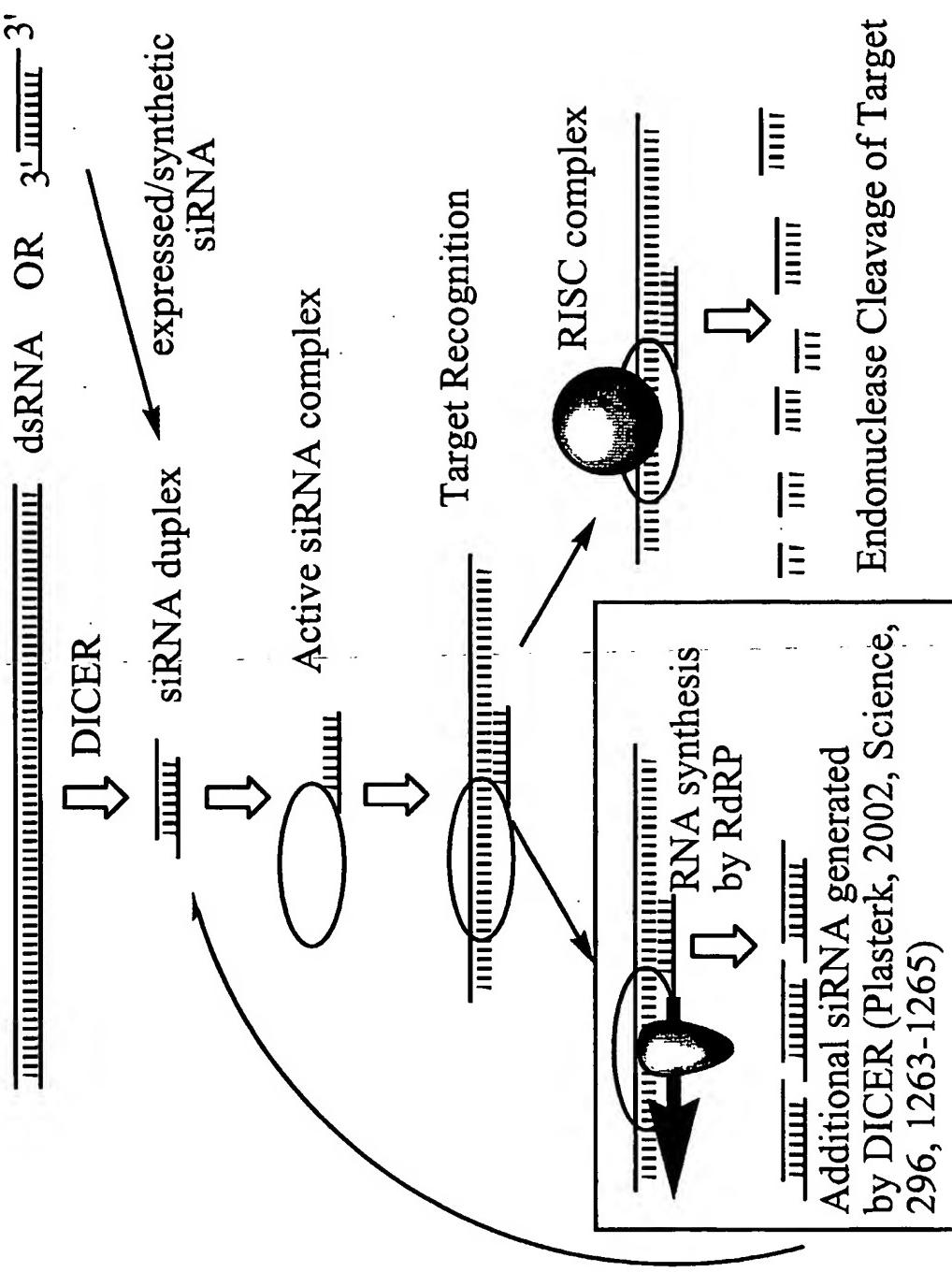
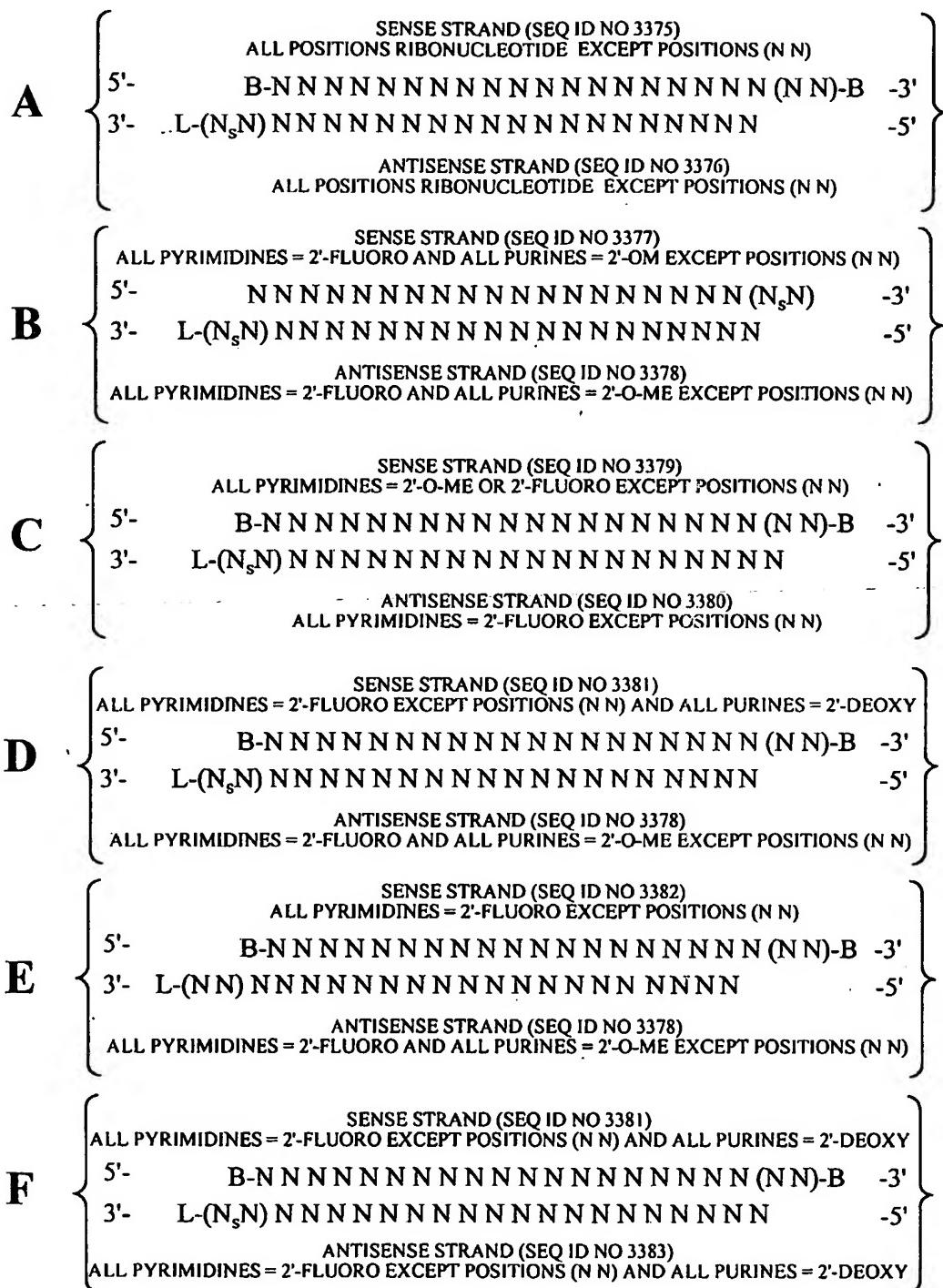
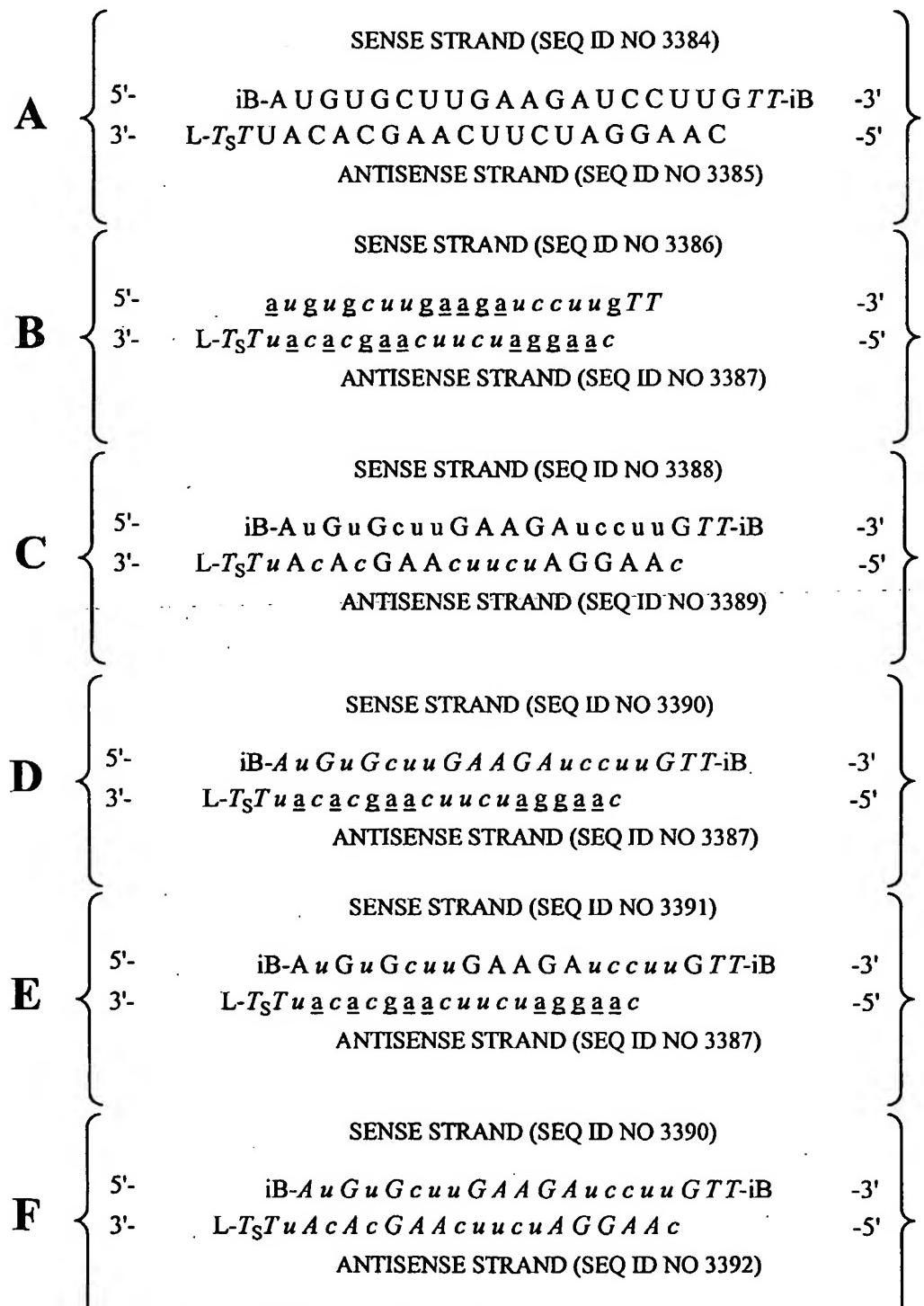
Figure 3

Figure 4



POSITIONS (NN) CAN COMprise ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALy PRESENTL = GLYCERYL or B THAT IS OPTIONALy PRESENTS = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionaly absent

Figure 5

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluoro

underline = 2'-O-methyl

ITALIC UPPER CASE = DEOXYiB = INVERTED
 DEOXYABASICL = GLYCERYL MOIETY or iB
 OPTIONAL PRESENTS = PHOSPHOROTHIOATE C
 PHOSPHORODITHIOATE OPTIONAL PRESEN

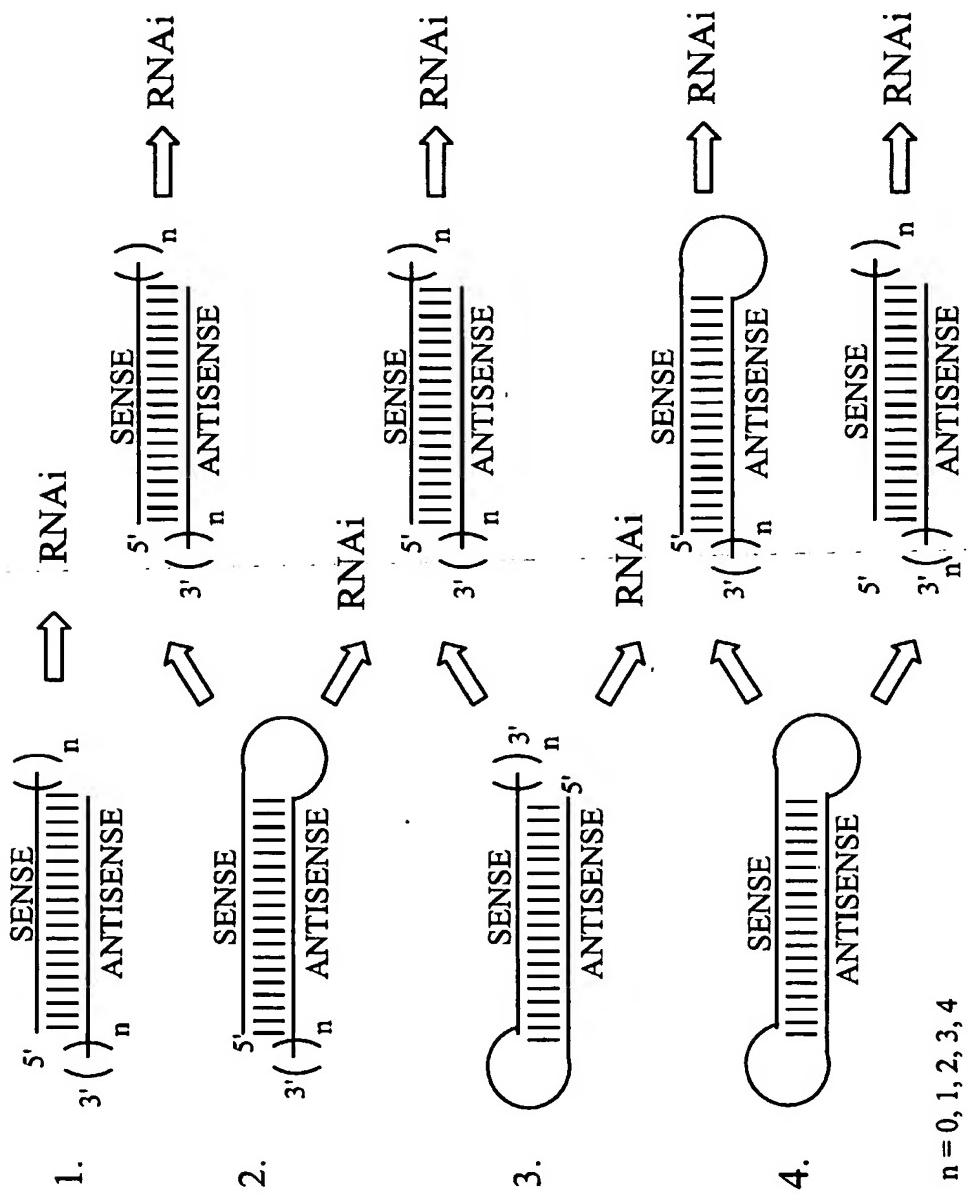
Figure 6

Figure 7

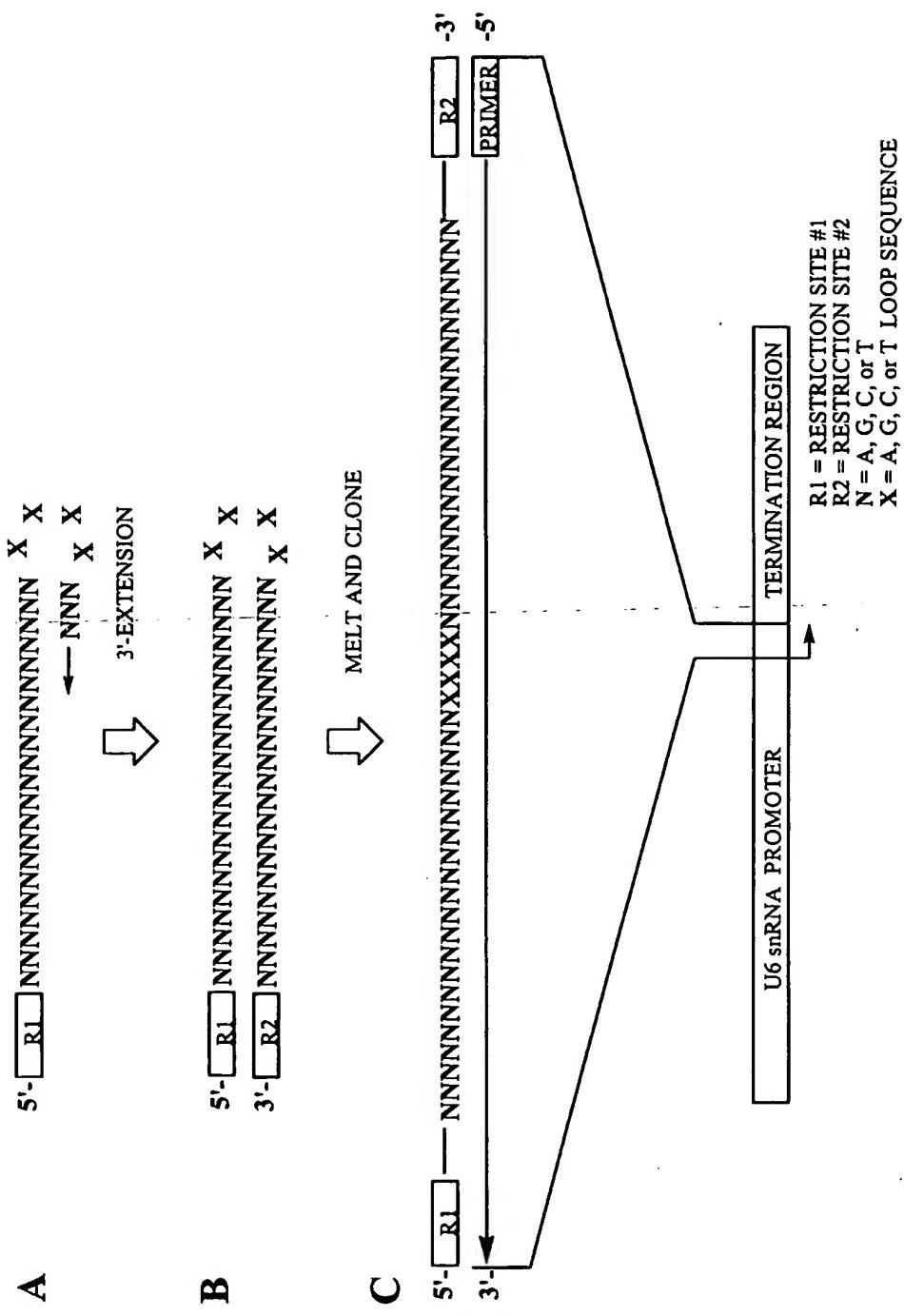


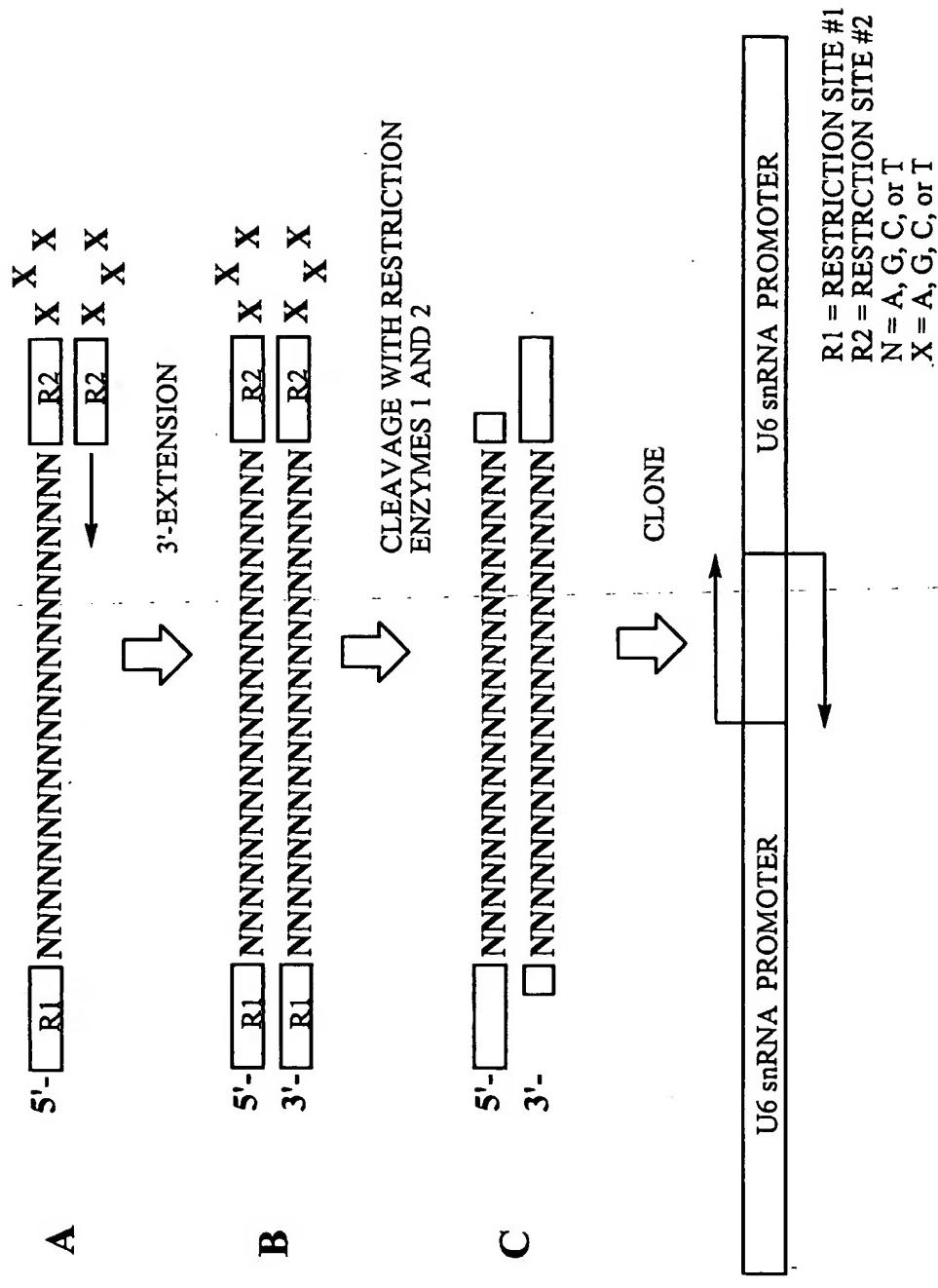
Figure 8

Figure 9: Target site Selection using siRNA

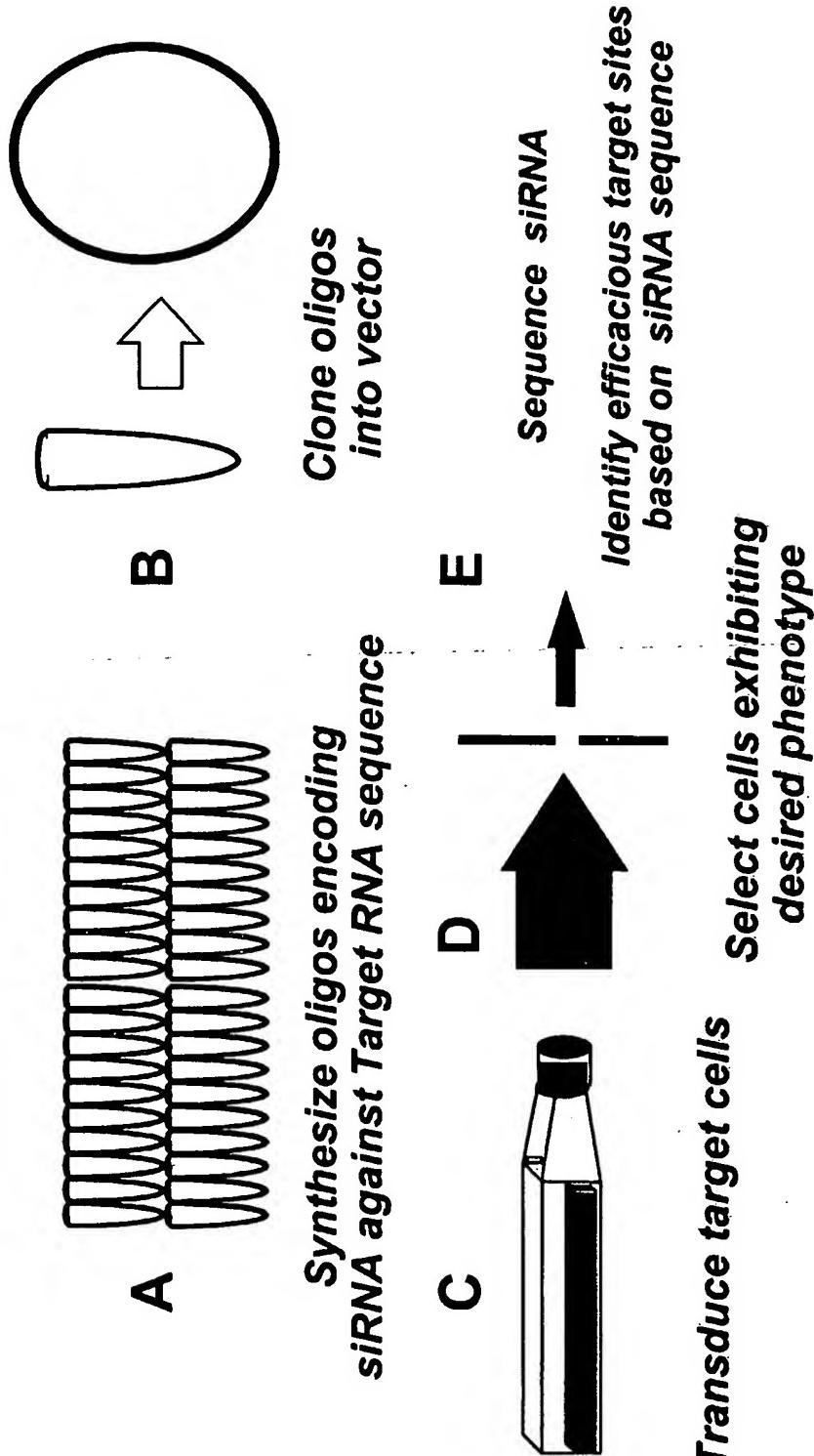


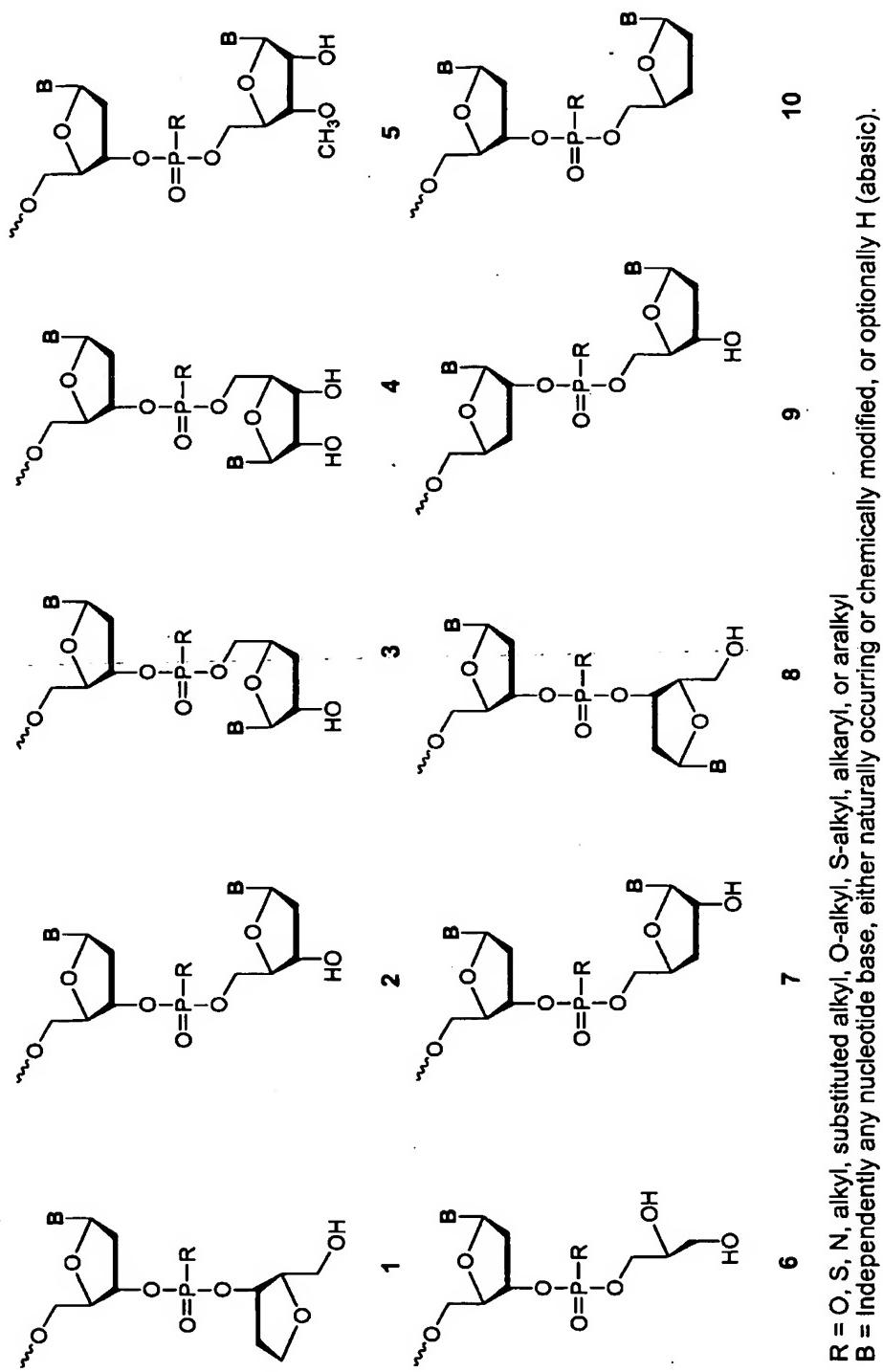
Figure 10

Figure 11: Modification Strategy

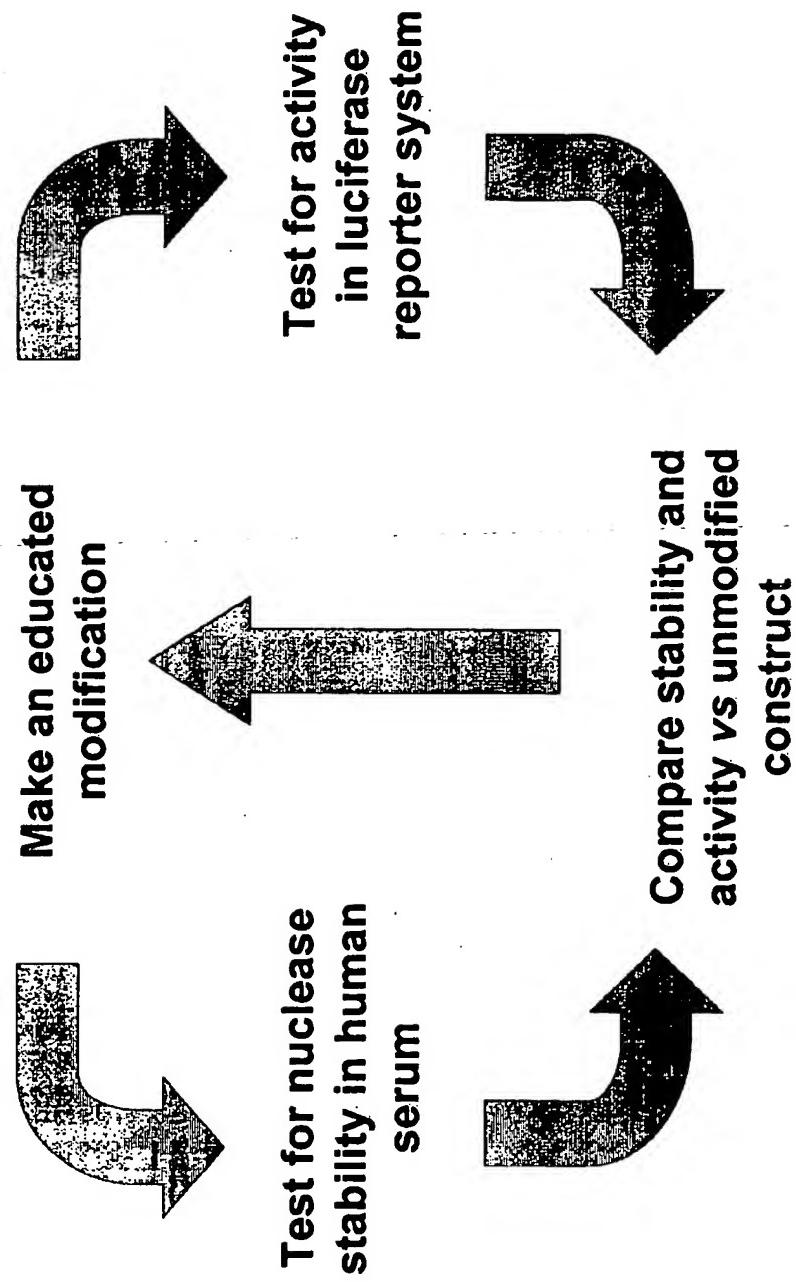


Figure 12: Phosphorylated siNA constructs

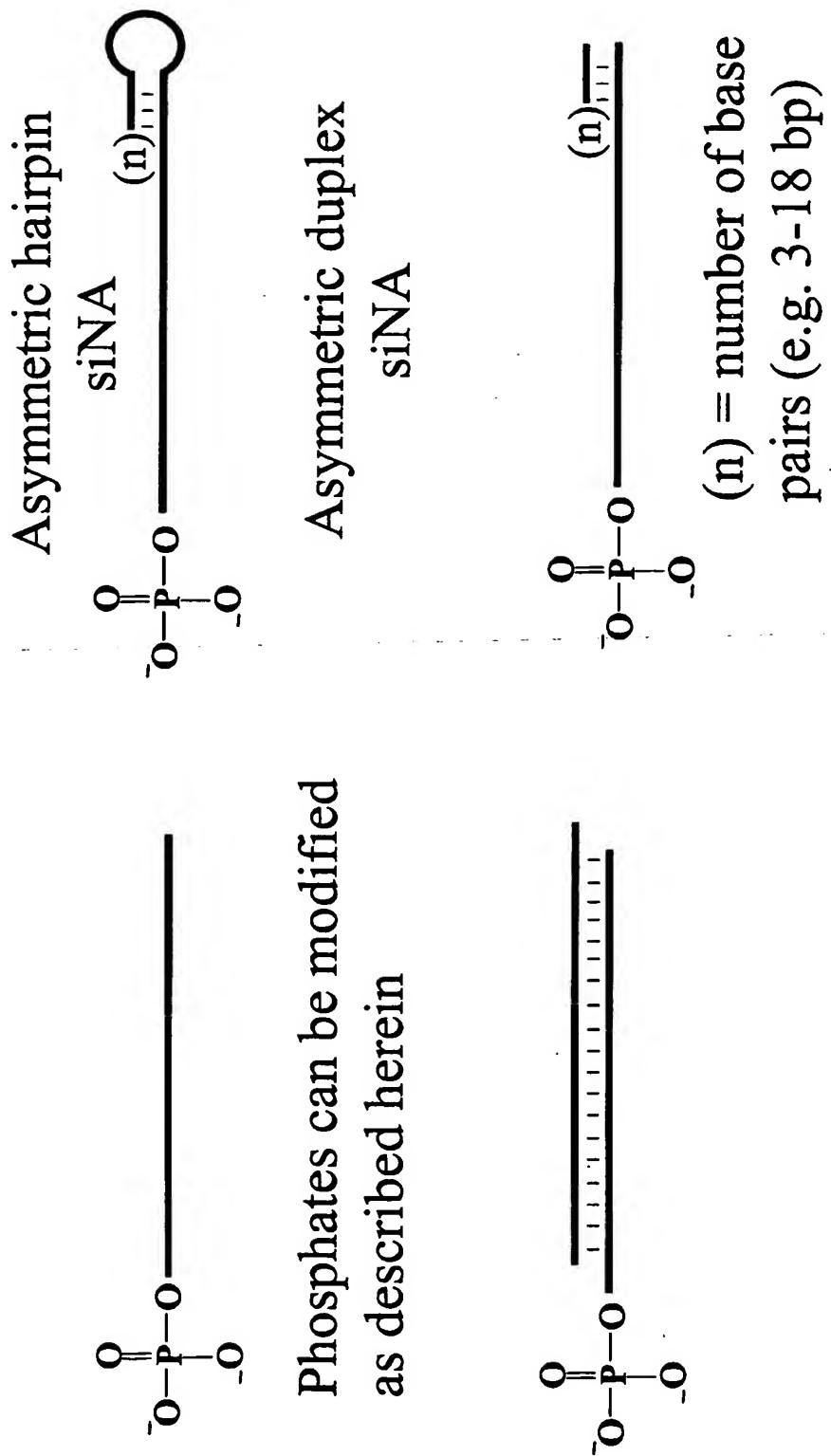


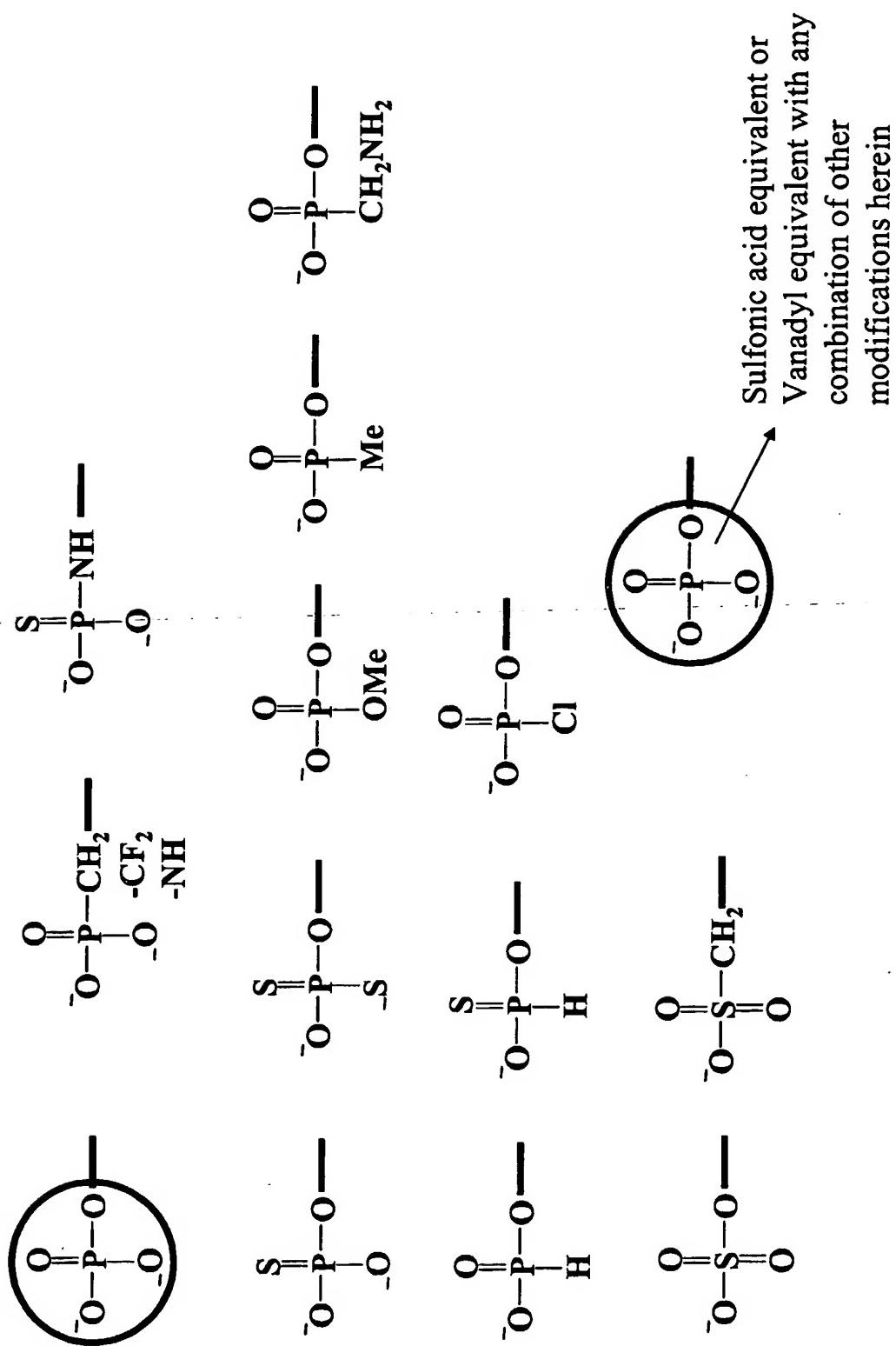
Figure 13: 5'-phosphate modifications

Figure 14A: Duplex forming oligonucleotide constructs that utilize palindrome or repeat sequences

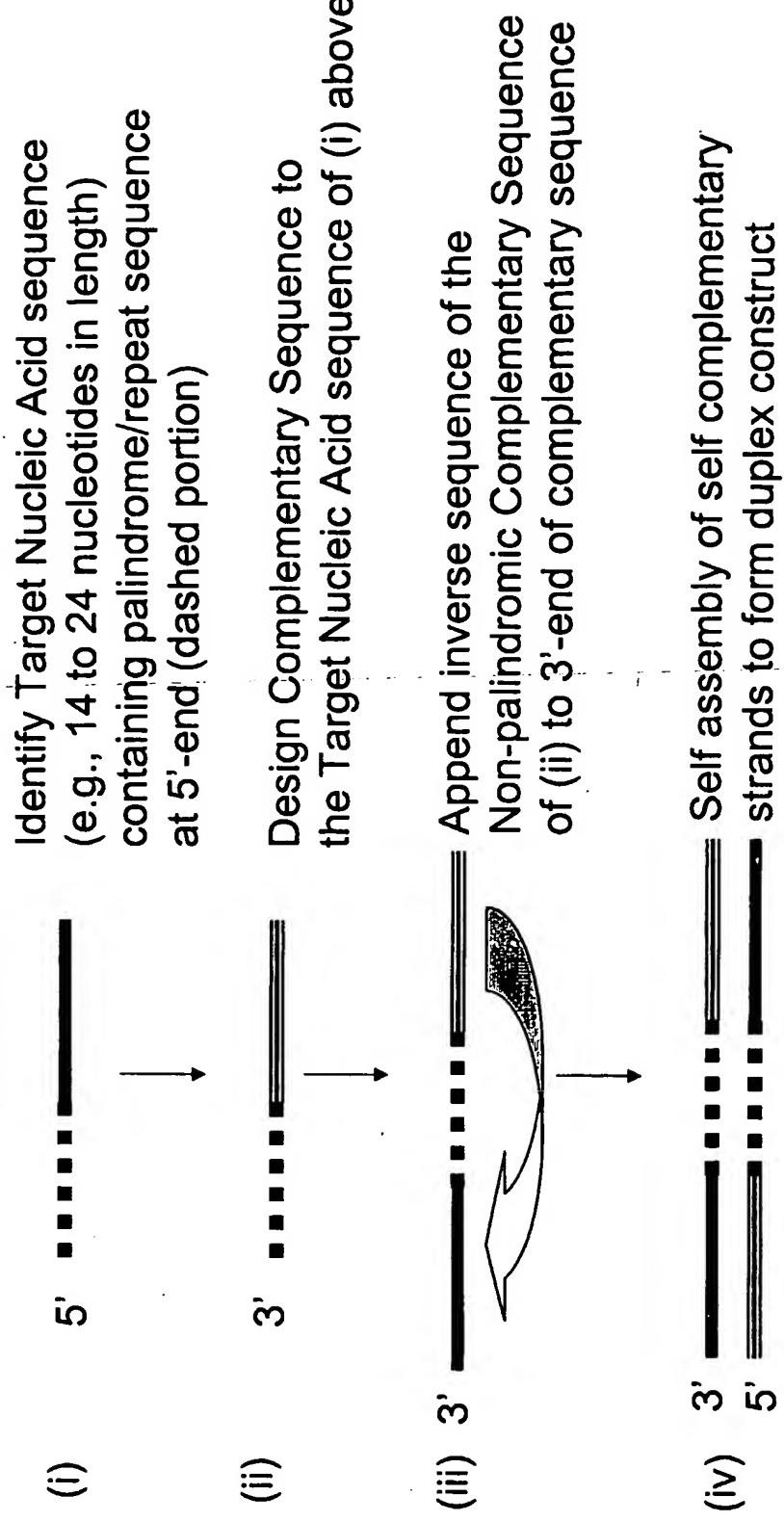


Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence

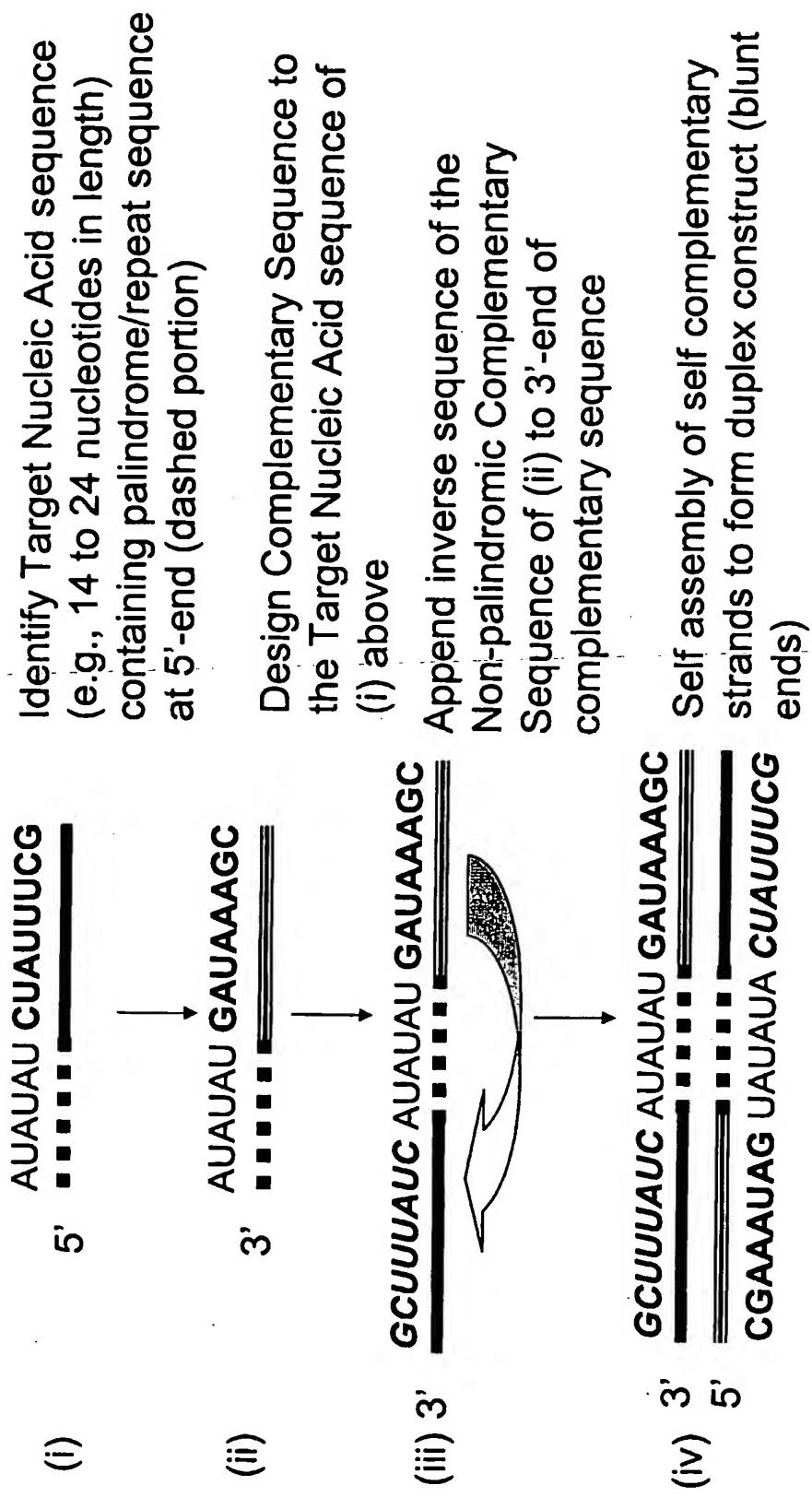


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

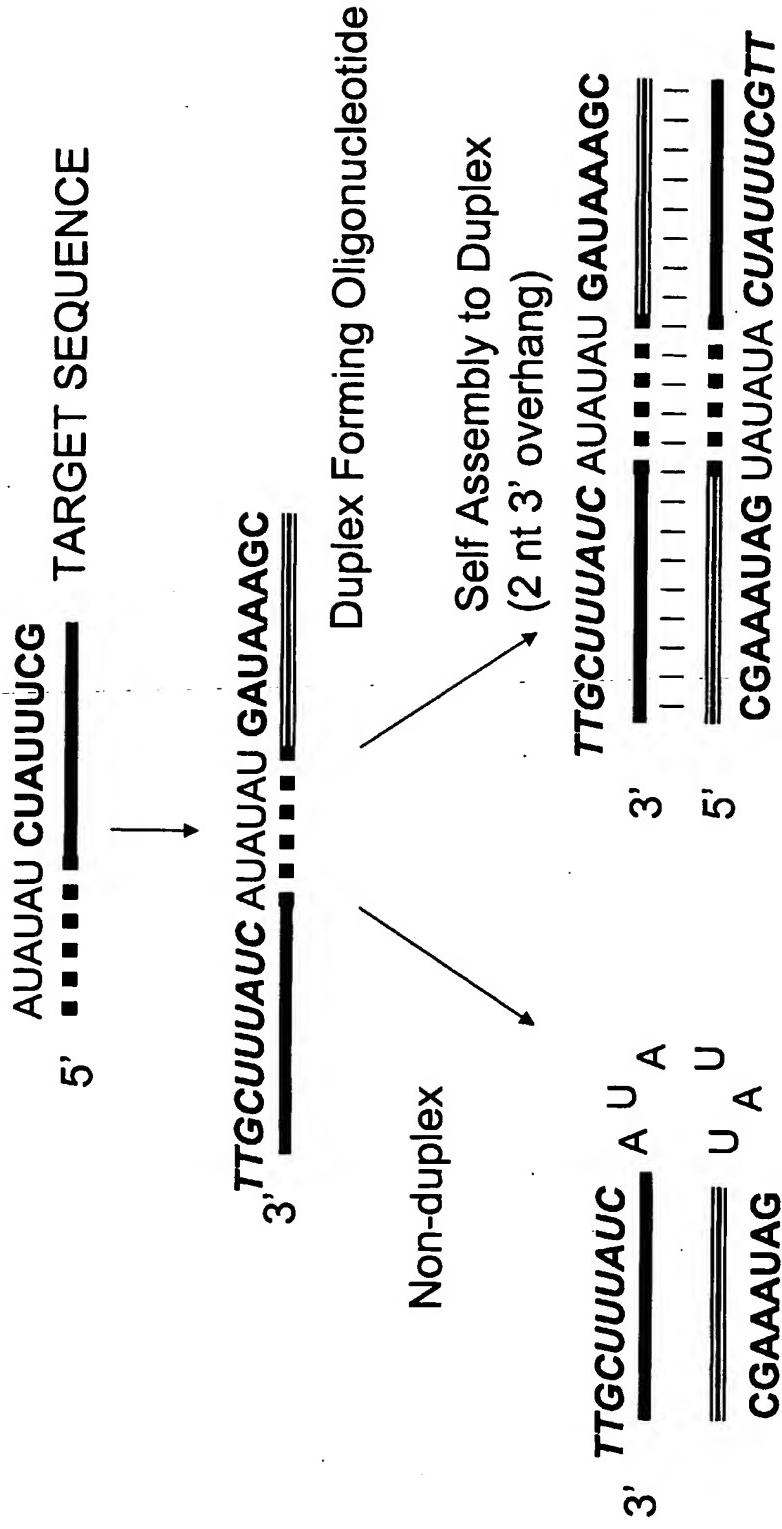


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression

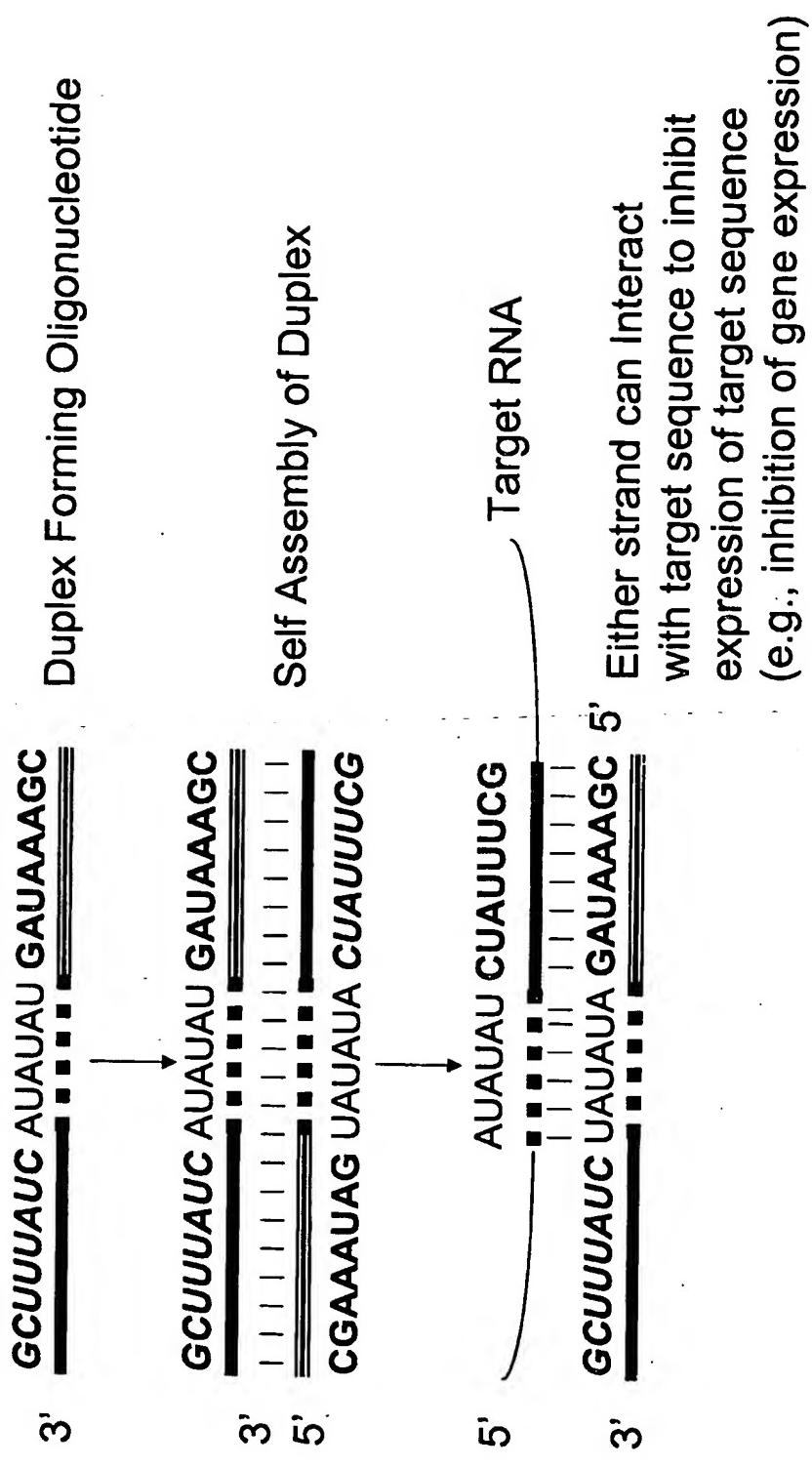


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences

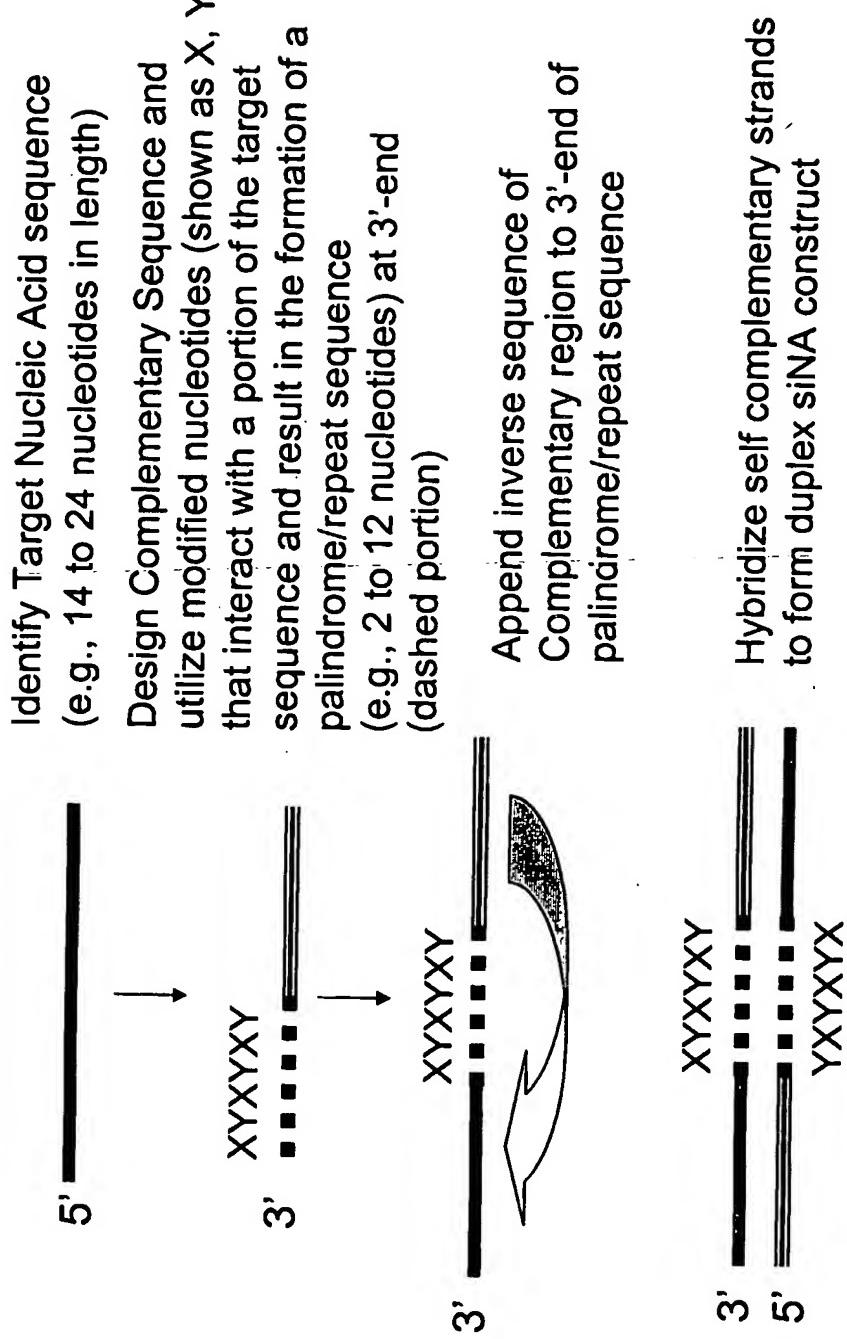


Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

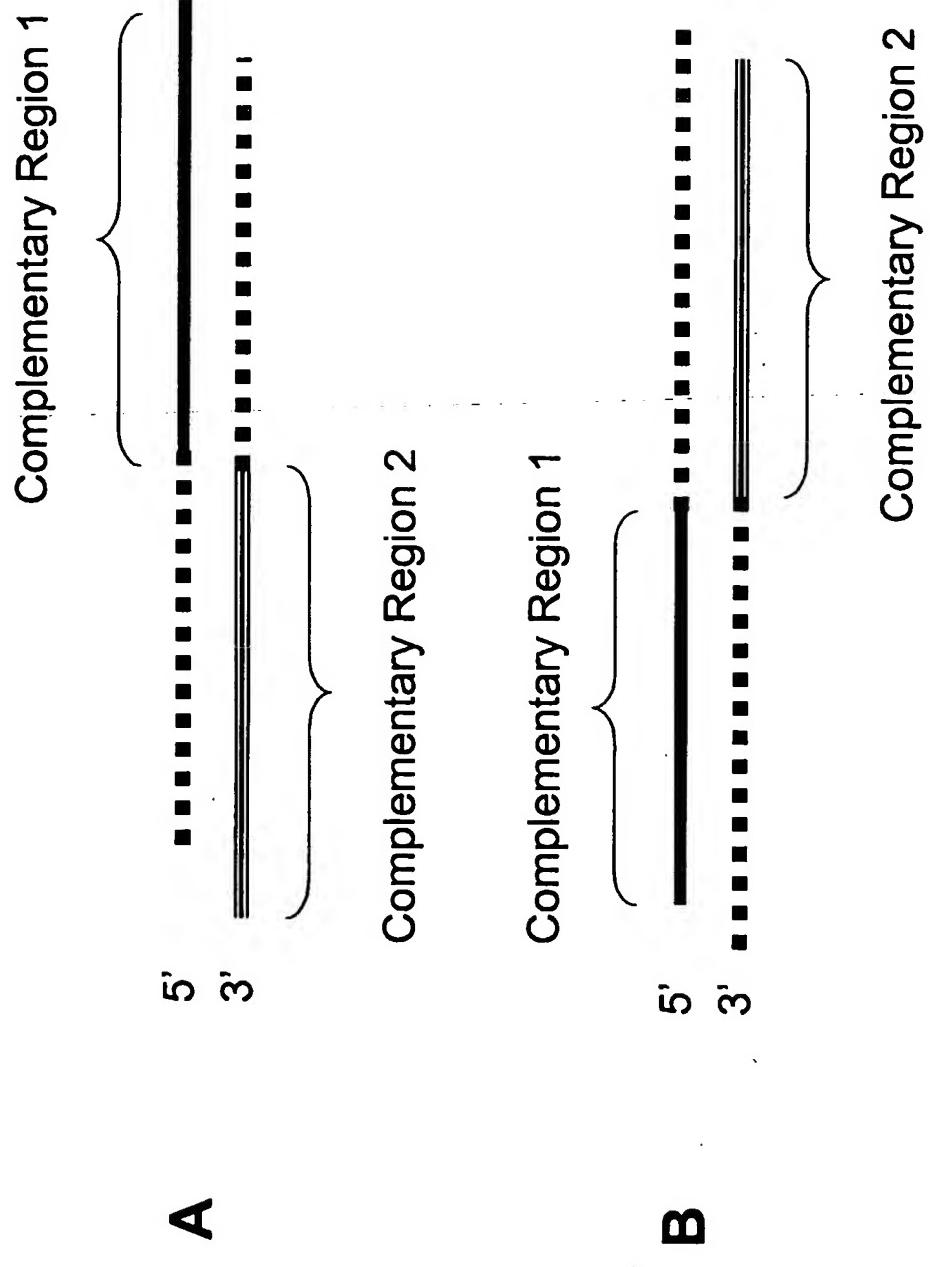


Figure 17: Examples of hairpin multifunctional siNA constructs with distinct complementary regions

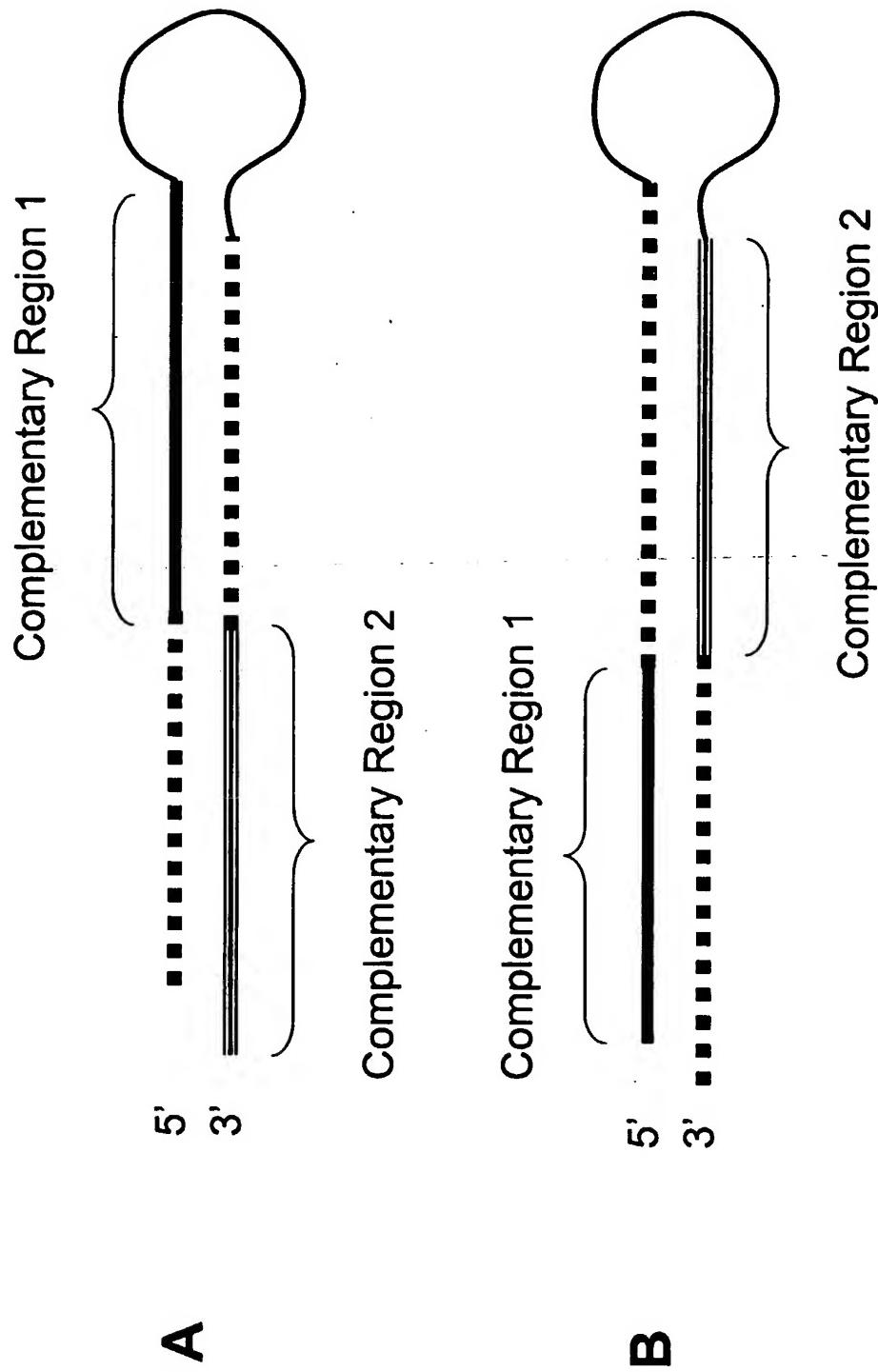


Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

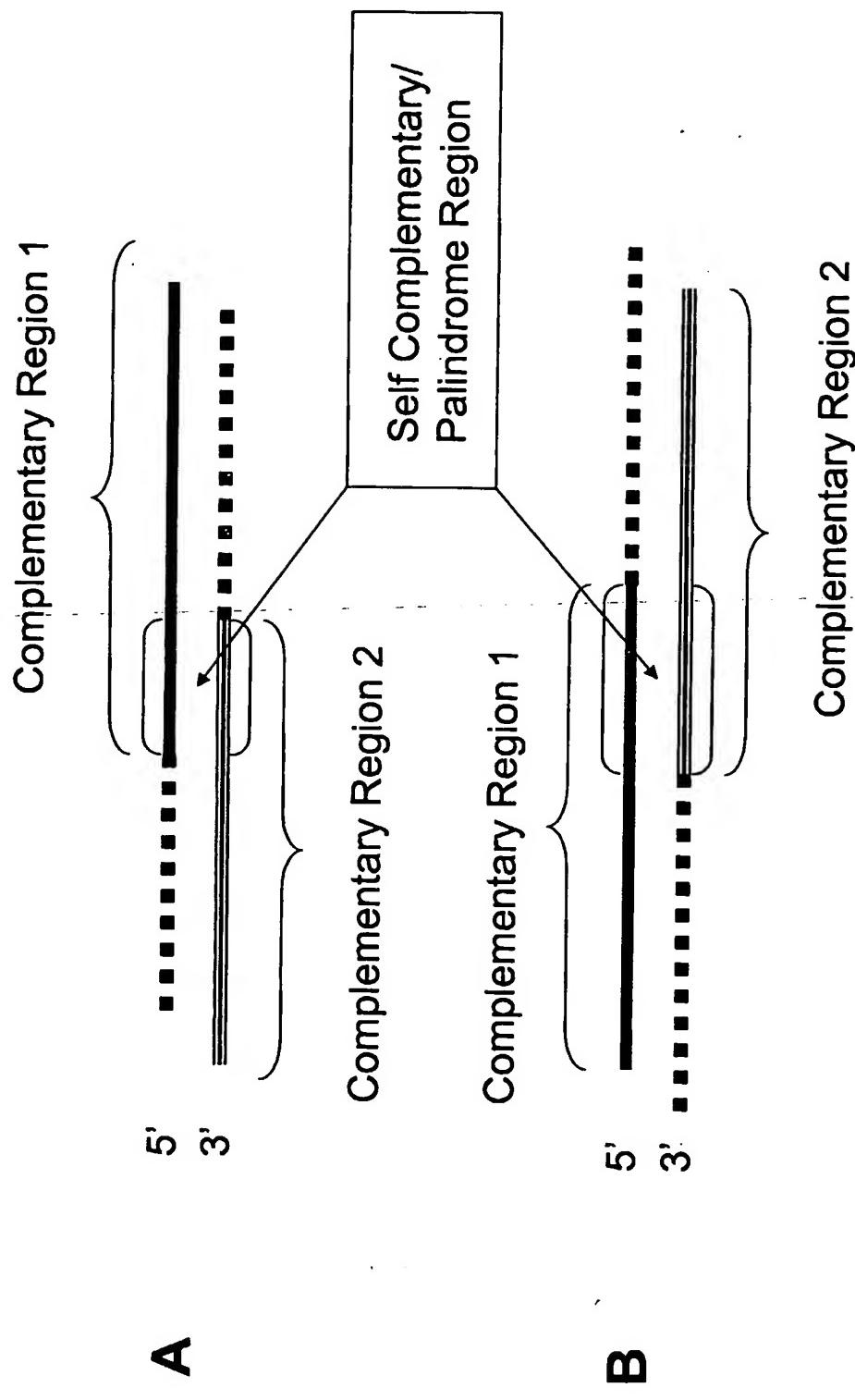


Figure 19: Examples of hairpin multifunctional siRNA constructs with distinct complementary regions and a self complementary/palindrome region

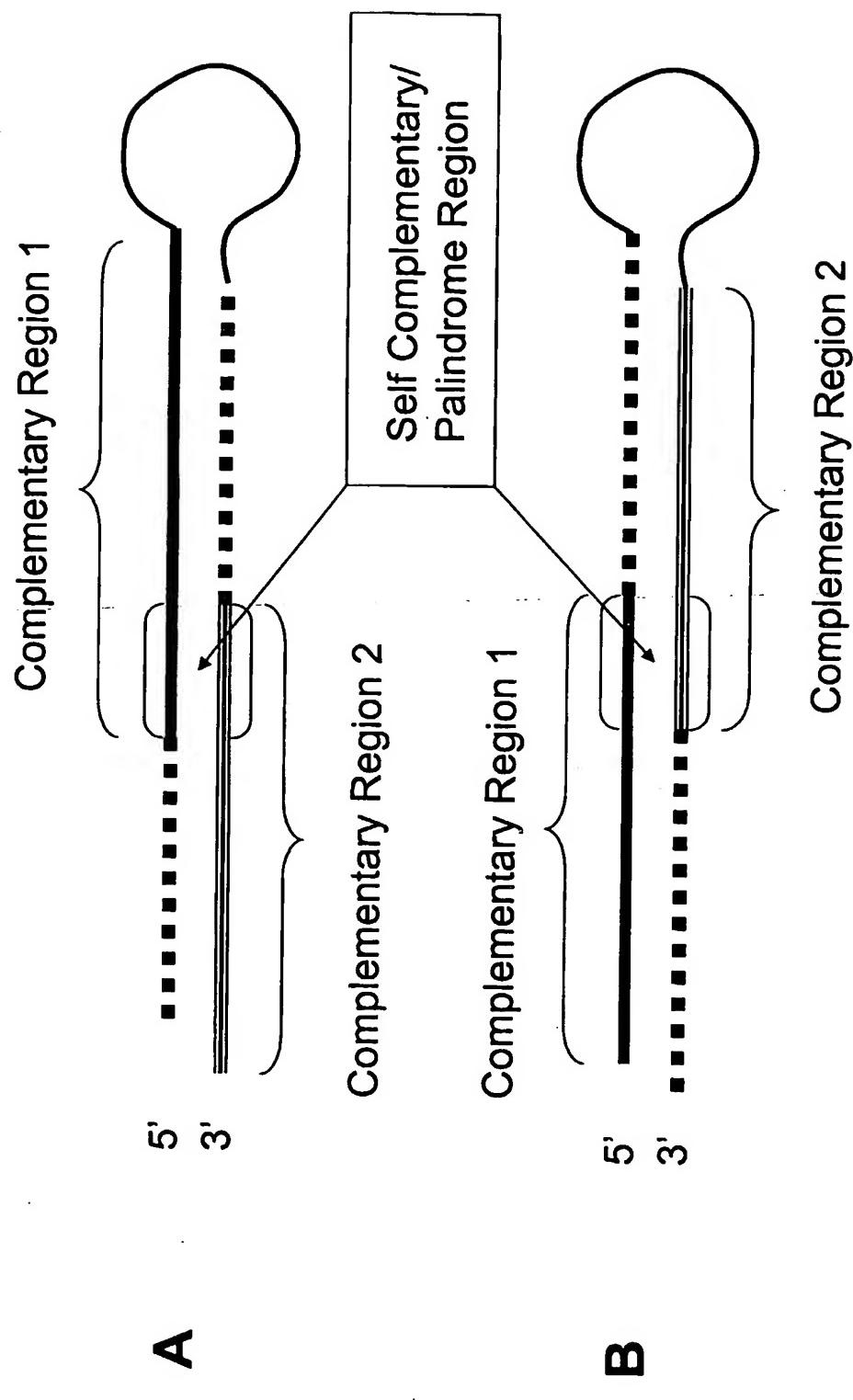


Figure 20: Example of multifunctional siNA targeting two separate Target nucleic acid sequences

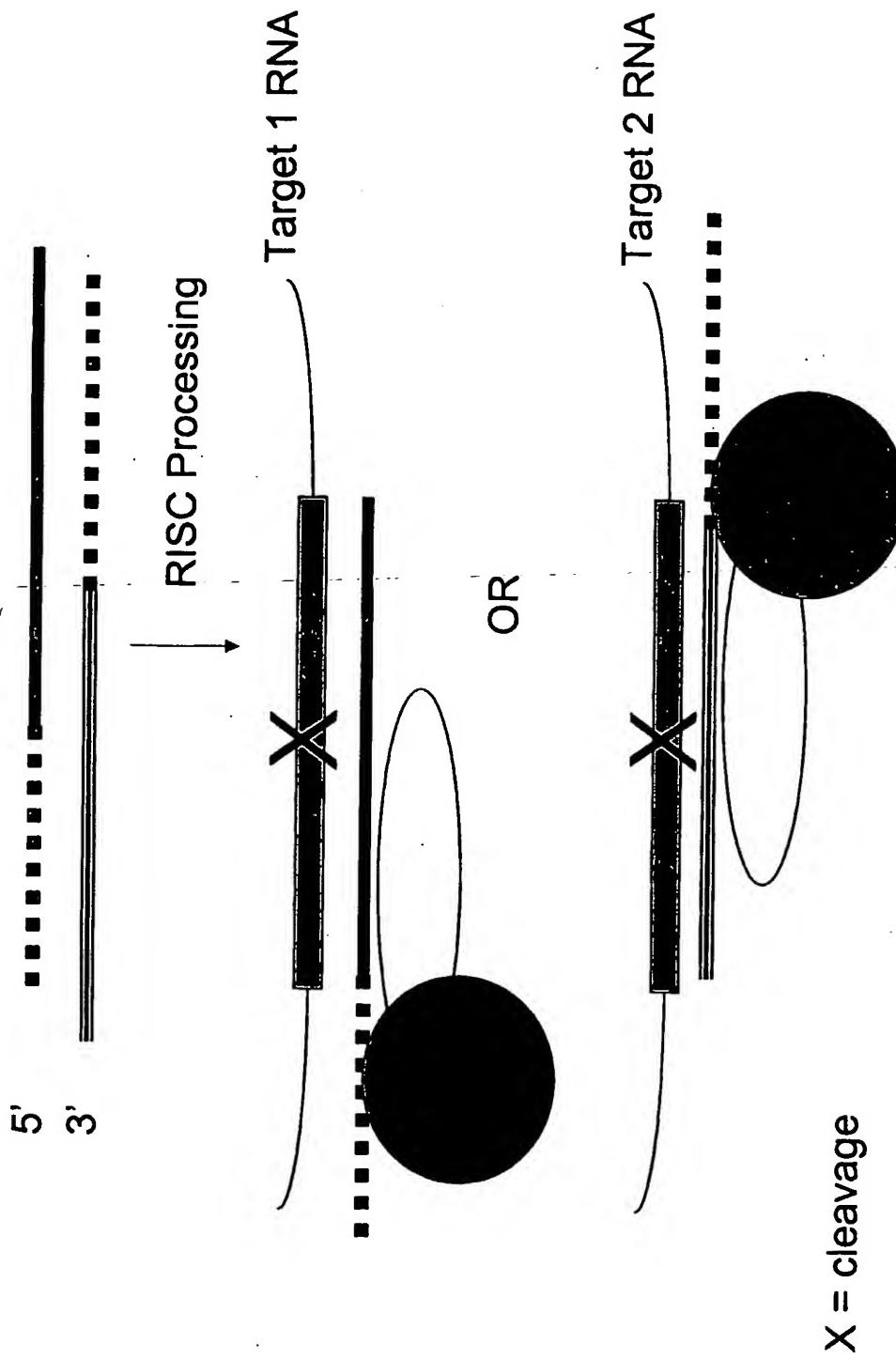


Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence

